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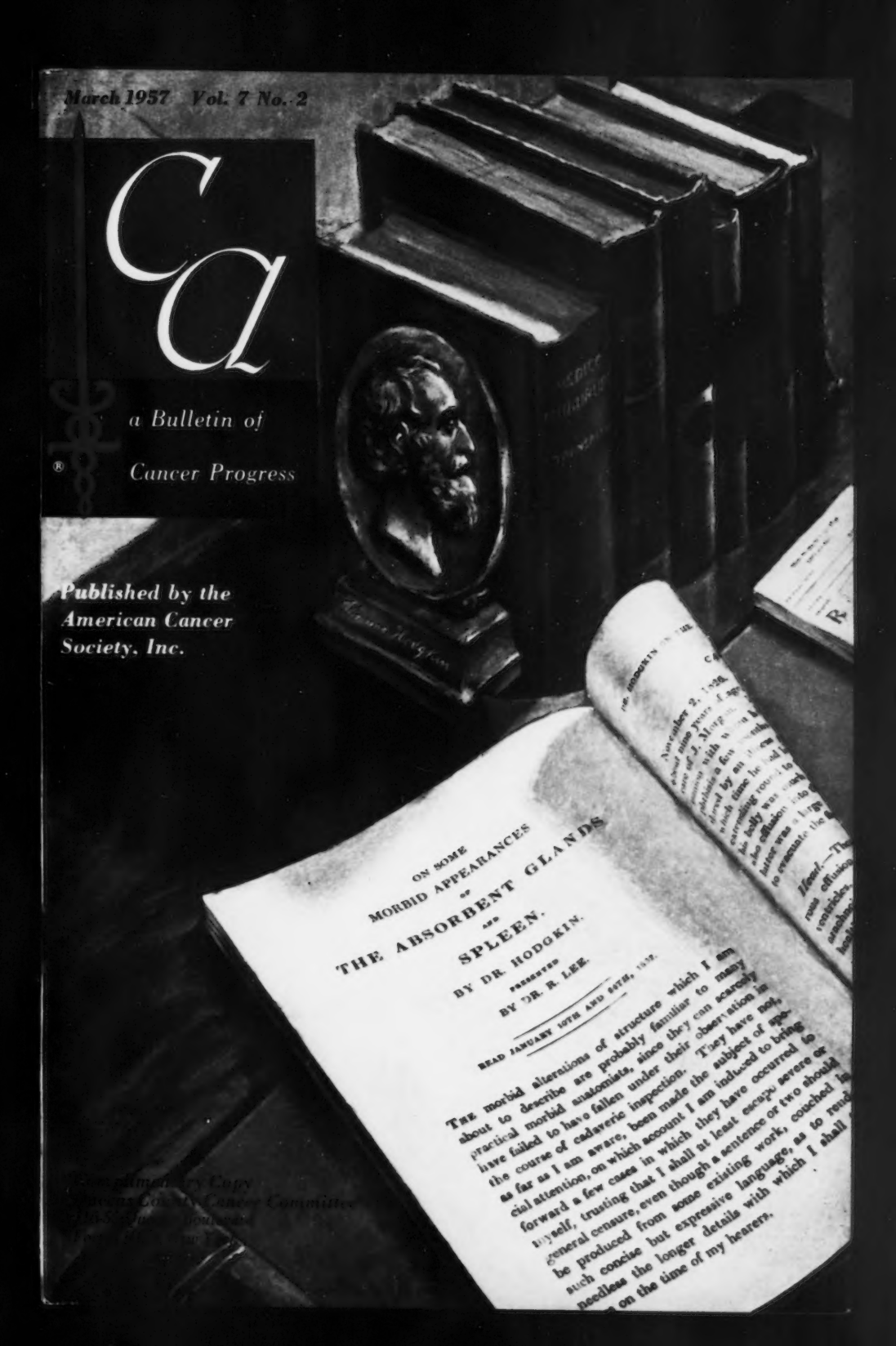

nothing to offer

"A pathological paper may perhaps be thought of little value if unaccompanied by suggestions designed to assist in the treatment, either curative or palliative; on this head however I must confess that I have nothing to offer." Thomas Hodgkin, in 1832, was referring to the hopeless prognosis in six patients with "morbid appearances of the absorbent glands and spleen"—a disease given his name by Wilks thirty years later, although Malpighi had outlined it two centuries earlier.

Today for tumors of the lymphoma group we still have "nothing to offer" as curative, although radiotherapy, chemotherapy, and occasional surgery can usually provide reasonable palliation and often prolong life.

Progress has been made particularly in the leukemias. These diseases offer unique opportunities for research in chemotherapy, for the results of therapy may be followed quantitatively by technically simple examinations of bone marrow and blood.

Much of the hope for the eventual control of cancer—discovery of its causes, of its cures, and, best of all, of how to prevent it—lies in comprehensive studies of the leukemias, including the mechanism of action of the many known chemotherapeutic agents, development of still more effective agents, and the how and why of acquired resistance to these agents in the leukemic cell.

Cover—

Thomas Hodgkin (1798-1823): On some morbid appearances of the absorbent glands and spleen. Tr. Med.-Chir. Soc. London 17:68, 1832.

During one of several pilgrimages to the Holy Land with his philanthropist friend, Sir Moses Montefiore, Hodgkin grew a full beard. Upon his return to London one of his students quipped that he went out with Moses and returned with Aaron.

These silver medals, the American Cancer Society's Annual National Award for distinguished service in cancer control, were presented to Dr. Gioacchino Failla, Professor of Radiology (Physics) and Director of Radiological Research Laboratory at the College of Physicians and Surgeons, Columbia University, and Dr. Edith Quimby, Professor of Radiology (Physics), College of Physicians and Surgeons, Columbia University. The Awards, presented at the Society's Annual Dinner at the Hotel Park Sheraton, New York City, on November 1, 1956, were in recognition of their pioneer work in developing precise methods of measurement of radiation dosage. Dr. Failla also pioneered in the design and construction of radium-emanation plants throughout the country and in protection against radiation injuries.

NEWSLETTER

MARCH, 1957

Endocrines and Cancer: reported from the Scientific Session, Annual (1956) Meeting of the American Cancer Society. Continued from January Newsletter:

Muhlbock (Amsterdam) said he believed that the selfsame hormonal (pituitary and ovarian) factors responsible for breast cancer in mice may be instrumental in the genesis of human mammary carcinoma. He feels that the hormonal response to emotions may play a part. In one set of experiments he established that mice isolated alone in cages developed spontaneous breast cancer sooner and with greater frequency than mice living under crowded conditions. He also found that mice given a chance to exercise at will (on a treadmill) had less and later breast cancer than non-exercising mice. He also told how dowdy, senescent bachelor mice rejuvenated and cleaned up when young females were placed in the cage with them.

Mueller (U. of Wis.) said that protein, lipid, and purine synthesis is accelerated up to fivefold when estrogen acts on uterine tissues. Li (U. of Calif.) said that human and monkey growth hormones are very similar but differ from bovine growth hormone. Gallagher (Sloan-Kettering) showed that tri-iodothyronine, a thyroid hormone, markedly potentiates the action of testosterone. Migeon (Johns Hopkins) reported that cortisol given in early pregnancy passes through the placental barrier and causes complete resorption of the fetus, while at term it brings on abortion.

Burt, Finney, and Scott (Johns Hopkins) produced what they described as a useful method of estimating and predicting the effect of therapy for prostatic cancer. It is based on the excretion of urinary hormones. High androgenic levels indicate that the patient will respond favorably to castration, estrogen, cortisone, or any combination of these measures. Low levels indicate there will be no response. When therapy is effective, urinary androgens fall.

Huffman (Oklahoma Medical Research Foundation) has screened 40 steroidal estrogens for antimitotic effects which might be of benefit in treating prostatic cancer. The hope has been to find a compound with weak estrogenic ac-

tivity and strong antimitotic properties. Preparations were tested against chick embryo fibroblasts and zebra-fish eggs. One preparation, judged promising from its in-vitro performance, has been tested clinically; but it is too early to tell how it affects patients or their cancers.

Hertig (Harvard) said that about 90 per cent of patients with endometrial cancer have associated ovarian lesions hyperactive in producing steroid hormones. The hormones may be produced by cystic follicles of the non-ovulating ovary of the young, the cortical stroma of the old ovary, or ovarian neoplasms of feminizing mesenchymal type. He said about 4 per cent of endometrial cancer occurs in young women who, as a group, are sterile, often obese, diabetic, or with other endocrine stigmata and who, because of lack of normal ovarian cycles, complain of irregular and profuse uterine bleeding. The majority of the remaining endometrial cancers arise in post-menopausal patients who often have had irregular premenopausal bleeding associated with noncyclical ovarian function, he said.

Rawson (Sloan-Kettering) reported that certain thyroid cancers secrete an iodinated protein which has not been found in normal sera. He also has recovered from some cancerous thyroids a thyroglobulin which seems identical with that produced by irradiating normal thyroid tissue. His observations suggest that some functioning thyroid cancers have a defect in their capacity to hydrolyze thyroglobulin.

Among the more significant developments in basic research -- and who can foretell what application they may have to cancer control a few years hence? -- are:

Kornberg and others (Washington U.) have synthesized DNA.

Ochoa (NYU) and others have synthesized RNA identical in all tests to natural RNA.

Zamenhof and others (Columbia) have introduced pyrimidine analogues (uracil carrying bromine, chlorine, or iodine) into E.-coli DNA and produced bacteria 80 times normal length, 1½ times normal girth, 1,000 times more vulnerable to UV than the normal. The monsters had 8 times the normal number of nuclei but only average DNA content.

Klein and Klein (Columbia and NY Botanical Garden) incubated non-virulent A. tumefaciens in DNA drawn from the virulent strain and transformed the non-virulent into plant tumor inducers. (Continued after page 72)

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Keeping up

Synergism in Cancer Therapy

Surgery, radiotherapy, and chemotherapy, formerly used independently or sequentially, are now used in combined treatment of cancer with increasing frequency. Chemotherapeutic agents used in cancer therapy are hormones, anti-metabolites, antibiotics, and nitrogen mustard derivatives (alkylating agents). "Negative chemotherapy," removal of the sources of hormones upon which the growth of the tumor depends, by orchidectomy, oophorectomy, adrenalectomy, and hypophysectomy, is just as important as positive chemotherapy by administration of exogenous hormones and other chemotherapeutic agents. Oophorectomy and adrenalectomy are sometimes carried out simultaneously, as are orchidectomy and adrenalectomy, thus giving the host defense mechanism a better chance of destroying the neoplasm. It is possible also that some tumors may be dependent upon adrenal hormones for growth. It is also possible that some tumors may be dependent upon steroid hormones of the gonads and adrenal cortex and upon one of the pituitary hormones, as ACTH, prolactin, growth hormone, etc. If independence to steroid and pituitary hormones develops independently the chance of independent cancer cells arising is probably much reduced by removal of gonads, adrenals, and pituitary early in the disease. Synergistic treatment of the leukemias and lymphadenopathy should have advantages. Many cases of acute leukemia benefit from 6-mercaptopurine, amethopterin, and ACTH or cortisone. Eventually, resistance develops to all. Amethopterin, ACTH, and cortisone are so toxic that they cannot be used continuously for very long. Combined treatment of acute leukemia must therefore await the availability of other drugs as non-toxic as 6-mercaptopurine. It is probably advisable to reserve the antifolic acid compounds and cortisone or ACTH for the terminal stage of the disease, although good results have been obtained from the combined use of cortisone and 6-mercaptopurine. The combined use of myleran with 6-mercaptopurine or with sodium arsenite in chronic leukemia should be worth consideration. Urethane, though effective, cannot be tolerated for long periods. Combined treatment of lymphadenopathies with CB 1348 and radiotherapy is sometimes effective. Increasing knowledge of the metabolic processes of cancer and leukemic cells should lead to the discovery of effective anti-metabolites, operating through mechanisms different from alkylation, which could be used in continuation with known agents over long periods, and might eventually allow the control of neoplastic growths.

Boyland, E.: Synergism in cancer therapy. Proc. Roy. Soc. Med. 49:877-879, Nov., 1956.

Antiandrogenic Treatment of Prostatic Cancer

Advanced cancer of the prostate is not cured by orchiectomy and estrogen therapy, but life is prolonged, pain and suffering are alleviated, and the size and consistence of the tumor and often its distant lymphatic, osseous, or pulmonic metastases are remarkably influenced in enough cases to warrant this treatment in every advanced case. In most clinics 90 to 95 per cent of the cases seen are advanced. It

with Cancer

is unusual to see an early case with a stony-hard, asymptomatic nodule, usually discovered at routine rectal examination, and without extracapsular extension, bone metastases, or increase in serum acid phosphatase. From 1941 to 1945 at the Massachusetts General Hospital sixty-four patients with advanced carcinoma of the prostate were treated by orchiectomy, oral stilbestrol, 5 mg. daily, and transurethral resection when indicated. All but two of the sixty-four were followed for ten years and these two were calculated as having died of prostatic carcinoma within the ten years. Survival was reckoned from the time of orchiectomy, not of the onset of symptoms. Eighteen of this group had bone metastases, and none of these survived for ten years. Five of the remaining forty-six died of unassociated causes. Seven of the remaining forty-one (17 per cent) lived for ten years or longer. The five-year–survival rate in a group of 127 patients without bone metastases was 46.1 per cent, and of these five-year survivors, only 39 per cent lived for ten years or longer after antiandrogenic treatment.

Ganem, E. J.: Advanced prostatic carcinoma; a study of ten-year survival after antiandrogenic treatment. New England J. Med. 254:1086-1087, June 7, 1956.

Palliation by Pituitary Implant of Radon

The pituitary gland was destroyed in twenty-five cases of advanced cancer of the breast and eight cases of advanced cancer elsewhere in the body by implantation of gold seeds containing radon. This was done by a cannula through the nostril and sphenoid sinus, with repeated roentgen-ray checks. In the last seven cases, better distribution of the seeds and more homogeneous irradiation of the gland were obtained by using two cannulas one through each nostril, and two seeds of 8 mc. each inserted to lie symmetrically, one on each side of the mid-line. No death occurred attributable to the treatment. Aside from transient headache in a few patients, the only complication—a formidable one—was radiation damage to the optic tract. In four cases there were defects in one visual field one to four months after the implant; in three of these there was complete loss of vision in one eye, and in the fourth complete blindness resulted. All patients had metastatic spread to lymph nodes, bones, lungs, or brain. The disease had progressed in all, in spite of surgery and radiotherapy. Several had received hormone treatment. The first patient had undergone adrenalectomy without success and the pituitary implantation so promptly reduced the 17-ketosteroid output (that had been but little affected by adrenalectomy) that the authors felt justified in performing the radon pituitary implantation in the remainder of the series without previous adrenalectomy. After implantation evidence of hypopituitarism develops in a few weeks. The urinary excretion of 17-ketosteroids falls below 1 mg. per day and the follicle-stimulating hormone to near zero. Usually 25 mg. of cortisone is required daily. The only favorable results were in seven of the twenty-five breast-cancer cases; no benefit resulted in the other eighteen cases of breast cancer, in the four cases of malignant melanoma, in the three cases of carcinoma of the uterus, or in the single case of sarcoma of the breast. Among the benefits derived from the implantation of

radon seeds were prompt relief of pain, particularly from skeletal metastases; recalcification of the affected bones; shrinkage of soft-tissue deposits; and even reduction in size of the primary growth. In only two of the seven cases coming to autopsy was the pituitary gland completely destroyed without damage to the optic tract. The authors suggest that some less penetrating isotope, as yttrium 90, may prove advantageous. The loss of sight may have to be accepted as an unavoidable risk, worth taking as an alternative to loss of life, on account of the small size and great depth of the sella turcica and the wide variations in the anatomical situation of the chiasma.

Forrest, A. P. M.; Brown, D. A. P.; Morris, S. R., and Illingworth, C. F. W.: Pituitary radon implant for advanced cancer. Lancet 1:399-401, April 14, 1956.

Radioactive Chromic Phosphate in Cancer of Bladder and Prostate

Radioactive colloidal gold was the first isotope to be used in treatment of far-advanced cancer of the prostate. Undesirable results have followed its use, such as radiation ulcer of the rectum or urinary bladder and depression of the hemopoietic system. Experience with roentgen-ray, radium, and radon-seed gamma radiation has shown damage to adjacent tissues. Chromic phosphate containing radioactive phosphorus, $CrP^{32}O_4$, emits only beta rays. The energy of the beta particles from P^{32} is greater than that from Au^{198}. The maximum penetration of the beta particles from P^{32} is 8 mm. in tissue, the major portion of the radiation dose being delivered into the 2 to 3 mm. of tissue immediately adjacent to the injection depot. When uniformly injected, a dose of 100 microwaves of radioactive chromic phosphate in 0.1 cc. volume per gram of tumor tissue will exert marked radiation effect on cancers of the bladder and prostate. This dose gives definite and safe relief of bladder-irritation symptoms incident to such far-advanced urological cancers. No damage to the rectum, bladder, or bone marrow, such as has been reported with radioactive gold, has been observed. Better distribution of isotopes injected interstitially can be expected to give better curative results.

Moore, V.; Gamble, D., and Libby, R. L.: Experiences with radioactive chromic phosphate in urological tumors. A.M.A. Arch. Surg. 72:464-468, March, 1956.

Cervical Cancer—Authoritative Appraisal

The author, one of the early advocates of surgery in the treatment of cancer of the cervix, considers surgery in no way a rival of radiation but as a partner. Results in the hands of experts will be good whichever method is used. Surgery cures radiation failures in a fair percentage of cases and radiation cures some of the surgical failures. Of great importance is the proper selection of cases for treatment by each modality. The recent studies by Graham and Graham of the sensitization response and the radiation reaction give objective evidence upon which to base selection of therapy in a given case. They say the sensitization-response changes are found in the benign basal cells, not in the cancer cells. The sensitization-response cells show dense, basophilic cytoplasm with fine vacuolization. The radiation reaction is found in the nonmalignant cells of the vaginal epithelium, and consists of multiple nuclei, increase in size, cytoplasmic vacuolization, and nuclear changes. It was found that those patients with a good response in the normal vaginal cells to radiation were cured in a very much higher percentage than those showing no response. Patients with a good percentage of sensitization-response cells were selected for treatment with radiation, otherwise surgery was used. Possible racial differences in reaction to irradiation and malnutrition are suggested to explain differences in results of treatment of cervical cancer in different countries. Radiation, potent for cure, is also a very destructive and injurious weapon and should be used with the greatest care. Similarly, surgical treatment is too frequently followed by injuries to the bladder and rectum resulting in fistulas. A 100-per cent follow-up of 622 cases from 1942 to 1949 showed 280 (45 per cent) five-year

"cures." At least 80 per cent of early invasive and 50 per cent of all cases of cancer of the cervix should be cured. As in other forms of cancer, early diagnosis and proper and prompt treatment should increase the cure rate.

Meigs, J. V.: Cancer of the cervix, an appraisal. Am. J. Obst. & Gynec. 72:467-478, Sept., 1956.

Cancer Survival Rates Improving

Analysis of 75,494 cancer cases, treated and untreated, listed in the Connecticut Cancer Register, from 1935 through 1951, shows marked increases in five-year–survival rates for patients with cancer of the cervix, corpus, prostate, large bowel, and endocrine glands. Earlier case finding and more effective use of available therapeutic procedures are factors in this improvement in outlook for survival. The seventeen years are divided into three periods of six, six, and five years for comparison of survival rates. The five-year–survival rates for all known male cases for the three periods were 12, 16, and 20 per cent, and for females 19, 27, and 32 per cent respectively; for the reported male cases 19, 22, and 25 per cent and for the reported female cases 29, 35, and 38 per cent, showing a definite, but diminishing rate of improvement. This is interpreted to indicate that further increases in survival must depend on better diagnostic and therapeutic methods. The five-year–survival rate for patients with remote metastases remained unchanged at 2 per cent during the entire seventeen-year period of the study. Patients with regional involvement showed rates of 18, 20, and 22 per cent for the three periods, and those with localized lesions 39, 44, and 51 per cent. Patients with localized lesions of the breast had survival rates of 65 per cent throughout the entire period, and those with regional involvement showed improvement of from 31 to 38 per cent. Cancer of the lung, all stages, showed improvement of survival of from 1 to 4 per cent.

Griswold, M. H.; Cutler, S. J., and Eisenberg, H.: Improvements in cancer survival rates. New England J. Med. 254:1062-1068, June 7, 1956.

Chemotherapy of Cancer

Alkylating agents (nitrogen mustard, triethylenemelamine, and triethylenethiophosphoramide) exert transient and feebly useful effects in chronic leukemia, Hodgkin's disease, and a few cases of bronchogenic carcinoma. Compounds with antifolic acid activity, aminopterin and amethopterin (methotrexate), purine antagonists such as 6-mercaptopurine, and cortisone together with its congeners evoke favorable reactions in children and some adults with acute leukemia. Variations in hormone balance induced by ablation of the gonads, adrenals, or pituitary, or by administration of exogenous gonadal, adrenal, and pituitary hormones or their synthetic counterparts give clearly beneficial effects in cancers of the breast and prostate. The chemotherapy of cancer is in its early phase and it is to be expected that the years to come will bring improvements.

Rhoads, C. P. (Chairman); Alpert, L.; Burchenal, J. H.; Karnofsky, D. A., and Pearson, O.: Chemotherapy in cancer. [Panel Discussion.] New York Med. 12:314-326, April 5, 1956.

Therapeutic Results in Breast Cancer

Few published results of treatment of cancer of the breast will stand up to really critical scrutiny. This includes many reports by notable authorities. We learn, for example, from Greenwood that the expectation of life for a woman with untreated cancer of the breast is 3.25 years, that treatment under "average conditions" increases the expectancy to 5.74 years, and under "best conditions" to 12.93 years. His figures were derived from other papers describing cases not treated because they were untreatable and his "best conditions" may have corresponded to the most favorable growths. Results are more closely related to the aggressiveness of the tumor and resistance of the host than to the conditions of treatment. The apparent good results of treatment are often explained by good selection not recognized by the reporting clinician. Surgeons are applying increasingly stricter standards of operability and then argue the merits of a

particular operation from their highly selected material. Proper appraisal of any treatment of breast cancer must be based on all possible information, including the catchment area of the hospital concerned and involving all factors influencing selection of patients. Over-all survival figures for all cases must be given. These should be year-by-year figures throughout the entire follow-up period rather than for arbitrary periods of three, five, and ten years. The age distribution of a series may greatly influence the crude survival figures. Adjustments must be made for age differences. There is great need for a reasonably simple, carefully applied and internationally acceptable system of clinical staging. It is regrettable that survival rate is often considered to the exclusion of the mutilation and morbidity of the more radical operations. Edema of the arm is three times as frequent in those patients whose axillas were dissected. Edema is also more common in those patients whose wounds fail to heal by first intention. More critical evaluation of published work would lead more surgeons to do fewer radical operations in the majority of cases of cancer of the breast. Until effective chemotherapy becomes available, surgeons should give more critical attention to quantitative and qualitative merits of their operative procedures.

Murley, R. S.: Carcinoma of the breast: the assessment of results. Canad. M. A. J. 74:427-432, March 15, 1956.

KINESCOPE 14: Lymphomas and Leukemias

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Lymphomas and leukemias account for approximately 8 per cent of all cancer deaths. These diseases are of importance to the practitioner since they may occur in any age group. The natural history of lymphomas and leukemias yields a great variety of clinical problems which require clarification.

In this program emphasis rests on the aspects of clinical and pathological diagnosis. The technique and use of bone marrow aspiration are presented.

The indications for radiotherapy and chemotherapy are discussed and appropriate case material is used to illustrate therapeutic regimens.

This kinescope is available through your Division of the American Cancer Society. Running time: 55 minutes; 16-mm. color with sound.

APPROVED FOR INFORMAL STUDY CREDIT BY THE
AMERICAN ACADEMY OF GENERAL PRACTICE.

at a glance . . .

one-minute abstracts of the current literature on leukemia and lymphoma . . .

Leukemia and Roentgen Therapy

Two series of patients with ankylosing spondylitis—1627 men treated by roentgen irradiation and 399 men treated by other methods—were compared for deaths from leukemia with the statistically calculated death rate from this disease in the general population. There was no death from leukemia in the non-irradiated group as against 0.17 death expected, and seven deaths in the irradiated group as against 0.33 expected. The odds against this excess of deaths being due to chance were greater than 1,000,000 to 1. This establishes that leukemia is associated with (1) ankylosing spondylitis, or (2) irradiation, or (3) ankylosing spondylitis treated by irradiation. In order to show that irradiation was the sole cause of the leukemia a larger series of non-irradiated cases would have to be studied. But certain it is that irradiation played the main part in production of the observed cases of leukemia. These results are confirmatory of those concerning the leukemogenic effects of atomic explosions, of irradiation for tumors and ankylosing spondylitis, enlargement of the thymus, and thyrotoxicosis, and of prenatal diagnostic irradiation previously reported.

Abbatt, J. D., and Lea, A. J.: The incidence of leukemia in ankylosing spondylitis treated with x-rays. Lancet 1:1317-1320, Dec. 29, 1956.

Parent Nursing in Leukemia

At the City of Hope Medical Center, a parent-participation program in pediatric oncology has been in operation since April, 1954. The program was started with particular reference to leukemia patients but it was soon made available to all children on the Tumor Wing. The program included screening and selection of parents, orientation of the parent to the nature and prognosis of the disease and to nursing duties, social service, schooling of the patients, occupational therapy and psychological services. The parent of the child facing inevitable death demands as much time as possible with the patient and is willing to participate in his hospital care. Their activity need not be restricted to menial tasks but may be extended to participation in hand feeding, forcing fluids, bathing, cleaning, diaper-changing, entertaining, reading, instructing, and amusing the children. Semiprofessional tasks are assigned as warranted. When the child is discharged the parent so trained is more efficient in home care and is more capable of giving the physician an accurate account of the course of the disease —temperature records, etc. In the past eighteen months not one parent was found emotionally incapable of accepting the nursing duties with a full knowledge of the inevitably fatal outcome. A not incon-

siderable aspect of value of the program is the avoidance of the resentment against the physician and the hospital so often arising in the parent of the hopeless patient—a resentment that often leads to the charlatan.

Bierman, H. R.: Parent participation program in pediatric oncology; a preliminary report. J. Chron. Dis. 3:632-639, June, 1956.

Leukemia, Lymphoma, and Psychology

Studies of the psychological factors in a group of males with lymphoma and leukemia made two years previously were extended to include a group of thirty-two women. Similar results were obtained in the two sexes. One of the "multiple necessary variant conditions" contributing to these disease processes may be separation from a key object or goal with ensuing depression. Various types of losses, separations, or threats of separation in a period four years prior to the apparent onset of the disease were found in all but two of these women and these two had been exposed to severe emotional trauma during the year preceding onset. The losses included loss of a significant person—mother, father, husband, or child. Menopause, natural or surgical, and change of home are also included. These losses, interpersonal stresses, emotional traumas, and personality characteristics are of significance not only etiologically but also in connection with exacerbations and duration of remissions in lymphoma and leukemia. An awareness of these findings by the physician is useful in the clinical understanding and management of patients with these diseases. The study is useful also as one basis for further research into the combinations of conditions necessary for the development of leukemia and the lymphomas. The psychosomatic aspects of these diseases warrant further study of larger groups, of both sexes, and of all ages.

Green, W. A., Jr.: Young, L. E., and Swisher, S. N.: Psychological factors and reticuloendothelial disease. II. Observations on a group of women with lymphomas and leukemias. Psychosom. Med. 18:284-303, July-Aug., 1956.

Treatment of Childhood Leukemia

More than half of the children now receiving treatment for leukemia will survive at least one year from the date of clinical recognition of the disease and 10 per cent of them for twenty months, but none is cured. Without modern treatment 50 per cent of leukemic children survived three and nine-tenths months and 10 per cent eleven months. Intensive use of supportive measures and recently developed chemical agents has prolonged the lives of leukemic children and made them more comfortable and happier. Before any treatment, the state of the renal function and possible respiratory-tract infection are to be determined; and cardiac, hepatic, and electrolyte status are to be studied throughout therapy. The method of treatment is determined by the physical state of the patient, the severity of the disease, the type of leukemia, and the response to initial measures. Steroids and antimetabolites should not be used under circumstances where they might mask the diagnosis. Emergency treatment is called for when there is a leukocyte count above 25,000 or below 2,000 and there is a definite, marked anemia. Emergency treatment consists of: (1) Intravenous ACTH, 25 mg. daily. (2) Oral hydrocortisone, 50 to 200 mg., or meticorten, 40 to 100 mg. (3) Transfusions of whole blood. (4) Appropriate antibiotics. (5) Sedation. (6) Maintenance of fluid and electrolyte balance. An effect is usually evident in two to five days. In the non-emergency, maintenance treatment the drugs of value are cortisone, hydrocortisone, meticorten, aminopterin, methotrexate, 6-mercaptopurine, and azaserine. The steroids give prompt, but not so long, remissions and should be reserved for emergency situations and complications. Patients given the folic acid, purine, and glutamine antagonists must be watched carefully for oral and cutaneous signs of toxicity and for changes in physical and hematologic state. Hemoglobin and white count are noted once or twice weekly, and the marrow is examined monthly. The frequency with which lymphosarcoma is followed by

leukemia suggests the possible value of using the chemotherapeutic agents after the conventional definitive treatment for lymphosarcoma with the object of preventing leukemia in these patients.

Dargeon, H. W.: Leukemia in childhood; current therapeutic considerations. New York State J. Med. 56:2079-2083, July 1, 1956.

Chlorambucil in Lymphomas and Leukemias

The aromatic nitrogen mustard, N,N-di (2-chloroethyl)-p-aminophenyl-β-butyric acid was used in the treatment of sixty-five patients with malignant lesions, including seven with lymphosarcoma, four with reticulum-cell sarcoma, seven with lymphocytic leukemia, and twenty-three with a variety of inoperable, solid tumors. The drug was given orally 0.1-0.6 mg./Kg. per day for one week to ten months, and was well tolerated. In lymphosarcoma and in chronic lymphocytic leukemia chlorambucil produced various degrees of remission in a significant number of patients. There was remarkable regression in size of tumors in one case of Hodgkin's disease after two months of continuous administration of the agent. There was little or no beneficial action in the metastatic solid neoplasms.

Hall, B. E.; White, L. P.; Smyth, J. D.; Tyan, M.; Willett, F. M.; Feichtmeir, T. V., and Farber, E. M.: Experiences with a new aromatic nitrogen mustard in the treatment of human neoplastic disease. Clin. Research Proc. 4:221-222, Sept., 1956.

Management of Leukemia

Leukemia is rarely encountered in general practice but the incidence is increasing. All forms of leukemia are fatal, but much can be done to relieve symptoms and to enable patients to be active for the greater part of their illness. It is no longer necessary to permit patients with chronic leukemia to spend their last years as unemployed invalids. Untreated acute leukemia is usually fatal within four months; 5 per cent of patients survive one year from the first appearance of symptoms. In the chronic form about half the patients survive three years—a few for many. Unexplained anemia not responding to hematinics is sometimes the first manifestation of acute leukemia. Other symptoms are: purpura, hemorrhage from the nose, gums, gastrointestinal or genitourinary tracts, and susceptibility to infection of the upper respiratory tract. Enlargement of the liver and spleen usually occurs later, although the spleen may fill the abdomen in less than two months. Symptoms of chronic leukemias do not occur until the disease is well advanced. In 1948 Farber obtained remissions in about one-third of the children treated with folic acid antagonists. Cortisone and ACTH are also effective. The nucleic acid antagonist, 6-mercaptopurine, sometimes gives remissions when resistance has developed to the other drugs. Acute leukemia should be treated in the hospital to provide for close attention to hematological detail—hemoglobin, total and differential leukocyte and platelet counts, bone-marrow examinations, etc. The agents of most value in chronic leukemia are: radiotherapy (including radioactive phosphorus), myleran (1,4-di-methane-sulphonyloxybutane), 6-mercaptopurine, TEM (triethylenemelamine), cortisone, and ACTH. In chronic myeloid leukemia, myleran or radiotherapy will bring relief; even grossly enlarged spleens become impalpable and severe anemia is relieved. If the patient becomes resistant to radiotherapy and myleran, 6-mercaptopurine may be given for many months, and is useful during the terminal "blastic" relapse. In chronic lymphatic leukemia, which is relatively benign, particularly in elderly patients, the objectives of treatment are: to combat intercurrent and recurrent infection, to reduce local lymph-node masses in relief of pressure symptoms, to prevent thrombocytopenia, and to relieve anemia. Oral antibiotics, as chlortetracycline and oxytetracycline, are the preferred antibiotics against infection. Radiotherapy is used for the lymph-node masses and the enlarged spleen. ACTH and cortisone, and radiophosphorus are sometimes effective in controlling the thrombocytopenia. For general use CB 1348, di-2-chloro-ethylphenyl-aminobutyric acid, a nitrogen mustard analogue, is preferred to

TEM. When the anemia fails to respond to transfusions, radiotherapy, and chemotherapy, splenectomy may be effective. Whether and when to operate should be a cooperative decision among the physician, the surgeon, and the hematologist.

Galton, D. A.: The management of leukemias. M. World 84:9-14, Jan., 1956.

Treatment of Acute Leukemia

In the management of acute leukemia it is recommended that the complete picture of the seriousness of this disease be presented to the patient or to a responsible relative. Therapy is initiated with blood transfusions and other supportive measures. In lymphocytic and unclassified leukemias prednisone or cortisone is used and continued in maintenance dosages as long as remission lasts. If after two weeks of hormone therapy there is no response, 6-mercaptopurine is added in adults, and an antifolic compound in children. When resistance develops to one agent another is tried. In granulocytic or monocytic leukemia the antimetabolites are used first, and one of the hormones is added if there is no remission in two or three weeks. In the dangerously ill patient 40 to 100 mg. of ACTH intravenously may be given daily together with an oral antimetabolite. This treatment as outlined for acute leukemia also applies in the terminal stages of chronic leukemia. About 50 per cent of children and 35 per cent of adults respond to this treatment, but the remissions are temporary and often short. There is no cure with our present methods of treatment.

Mills, S. D., and Stickney, J. M.: Management of acute leukemia. M. Clin. North America 40:1111-1115, July, 1956.

Treatment of Chronic Leukemia

Palliation of the symptoms of chronic leukemia may be obtained by therapy with various substances, but it is doubtful if treatment prolongs life. In chronic myelocytic or monocytic leukemias of the Naegeli type roentgen irradiation, radiophosphorus, urethane, nitrogen mustard, potassium arsenite, 6-mercaptopurine, TEPA, thio-TEPA, and myleran are useful. Of these roentgen irradiation and myleran are preferred as giving most satisfactory remissions with the least hazard. In chronic lymphocytic leukemia, chronic monocytic leukemia of the Schilling type, and in chronic reticuloendotheliosis roentgen irradiation, TEM, and nitrogen mustard are efficacious. Older patients with chronic lymphocytic leukemia without significant adenopathy or anemia do well without treatment, which is withheld until anemia, significant adenopathy, or other indication of impending crisis occurs. No known treatment prolongs the life of the chronic leukemic.

Watkins, C. H.: Treatment of chronic leukemia. M. Clin. North America 40:1117-1123, July, 1956.

Incidence of Leukemia

From abstracts of hospital records and death certificates of approximately 1700 leukemia patients in the Borough of Brooklyn in the period, 1943-1952, it was found that: The incidence of leukemia in white males was 71.3 and in white females 57.7 per million per annum, and for Negroes 46.5, and 30.6. Sex ratios were lower for acute than for chronic forms of the disease, and, in both acute and chronic forms, for myeloid than for lymphocytic cell types. Each type of leukemia has its own age incidence curve. The lymphatic forms are more sharply associated with the extremes of life than are the myeloid types. Acute lymphatic leukemia appears at a younger age than myeloid leukemia, and chronic lymphocytic leukemia at an older average age than chronic myeloid leukemia.

MacMahon, B., and Clark, D.: Incidence of the common forms of human leukemia. Blood 11:871-881, Oct., 1956.

Management of Lymphomas

The following chemical agents were used in the treatment of 221 patients with leukemia and other neoplastic disease of the hemic and lymphatic systems: nitrogen mustard, urethane, myleran, aminopterin,

potassium arsenite, stilbamidine, triethylenemelamine, cortisone, and ACTH. Of the 221 patients studied, seventy-nine had acute leukemias. In the remaining 142 the five-year survival from clinical onset was 27 per cent and from date of diagnosis, 14 per cent. A similar, previous series of 212 cases of myelocytic leukemia, 137 of chronic lymphocytic leukemia, 215 of lymphosarcoma, 226 of Hodgkin's disease, and 149 of acute leukemia, all treated primarily by radiation, was compared with the present series. No significant differences were evident, except that life was prolonged in acute leukemia, and this could not be attributed entirely to the use of the antifolic acid compounds. Presently available treatment, therefore, has no significant effect upon mortality in the lymphomas, although it does have marked palliative effects upon morbidity. Treatment, then, should be as conservative as possible in achieving the temporary benefits. The general medical management and the early and effective treatment of reversible complications and concurrent disease are as important as the specific chemotherapy.

Shimkin, M. B.: Chemotherapeutic management of lymphomas: effect upon survival. Acta Unio internat. contra cancrum 11:318-328, 1955.

Differential Diagnosis of Acute Leukemia

A child with a history of weakness, pallor, tiredness, and fever, and who has anemia with enlarged lymph nodes, liver, and spleen, and hemorrhagic lesions of the skin and mucous membranes may properly be suspected of having leukemia. But not all of these signs and symptoms are present in every case. Unexplained anemia, and leukocytosis or lymphocytosis often suggest the possibility of leukemia to the physician. Leukocyte counts above the adult level and preponderance of lymphocytes over neutrophils are normal in children less than 5 years old. The most common error in the diagnosis is to mistake acute infections — pertussis, rubella, mumps, pneumonia, etc.—for leukemia. Careful and repeated observations of the peripheral blood and the bone marrow will rule out leukemia when the child is actually suffering from other disease, a nutritional defect, intoxication, or severe hemorrhage. Many errors in diagnosis of leukemia could be avoided if the physician will acquaint himself with the normal total leukocyte counts and with the normal lymphocyte-neutrophil ratios from birth to adolescence. In cases of leukemia without leukocytosis the course of the disease may be followed by repeated examinations of the peripheral blood and the bone marrow.

Mills, S. D.: Differential diagnosis of acute leukemia in children. M. Clin. North America 40:1103-1109, July, 1956.

Leukemia and the Atom Bomb

The leukemogenic effect of atomic radiation has been well established by investigations on survivors in Hiroshima and Nagasaki. Up to January 1, 1954, ninety-two verified cases were reported in an exposed population of 216,176. The greatest number of cases of leukemia occurred in individuals exposed at 1000 to 1500 meters from the hypocenter. The peak occurrence of leukemia was probably reached in 1951. Although cases will continue to appear the rate of occurrence is definitely declining. Neutrons as well as gamma radiation were probably involved in leukemogenesis. Cytologic studies in the preclinical stage showed the early appearance of a small percentage of myelocytes and metamyelocytes and a very significant basophilocytosis. Separated leukocytes had extremely low alkaline phosphatase activity, even in the earliest stages of the disease. The acute and chronic myelogenous types of leukemia predominated.

Moloney, W. C.: Leukemia in survivors of atomic bombing. New England J. Med. 253:88-90, July 21, 1955.

Leukemia after Fifty

Fifty-seven per cent of 553 patients who died from leukemia were more than 50 years old. Sixty per cent of all leukemias were acute, and 46 per cent of

these occurred in patients over 50. The clinical, hematologic, and histologic features of acute leukemia in patients over 50 are distinctive and can be differentiated from those of acute leukemia in younger patients, and from chronic leukemia. Because of the usually brief clinical course following diagnosis, of its intractability, and of the high degree of immaturity of the pathologic leukocytes, this leukemia in patients beyond 50 should be termed acute, whatever the length of indefinite symptoms prior to diagnosis.

Few remissions are produced in adults by the therapeutic agents used successfully in children with acute leukemia. Nothing is known of the nature of the pathologic process that leads to the development of the disease. It may be the same as or different from that responsible for acute leukemia in children. The high incidence and its high mortality rate indicate the desirability for further research into its clinical features, pathologic background, and especially into its successful treatment.

Gunz, F. W., and Hough, R. F.: Acute leukemia over the age of 50: a study of its incidence and natural history. Blood. 11:882-901, Oct., 1956.

Phenylbutazone in Hodgkin's Disease

The antipyretic, anti-inflammation, and analgesic properties of phenylbutazone suggested its use in treatment of the major symptoms of Hodgkin's disease—adenopathy, fever, and pain. But the results are transient and partial, the symptoms returning some weeks or months after stopping treatment. Moreover, after many remissions given by phenylbutazone, definite resistance to it is developed as with all other drugs used in treatment of malignant lymphogranulomatosis. Used together with other drugs, alternating or combined, phenylbutazone is of value in the symptomatic treatment of Hodgkin's disease. During its use, water balance, blood picture, and especially digestive disturbances should be carelly watched. It should not be used in patients with cardiorenal or liver disease. The dose used for treatment of the attack was 0.5 to 1 Gm. per day, and for maintenance 0.2 to 0.5 Gm. A review of forty-seven cases from the literature is presented.

d'Alteroche, J.: De l'intérêt thérapeutique de la phénylbutazone au cas de la lymphogranulomatose maligne. [Phenylbutazone in Hodgkin's disease.] Paris. R. Foulon. 1955; pp. 1-54.

Response to Leukemia Treatment

The Clinical Studies Panel of the Cancer Chemotherapy National Service Center formulates precise definition of response to treatment of acute leukemia so that better comparison may be made of results among patients treated with different drugs and by different physicians. Preliminary criteria for evaluation of response are suggested. Response is evaluated as 1, excellent; 2, fair; and 3, poor, as shown by A, marrow; B, peripheral blood; C, physical findings; and D, clinical symptoms. Detailed specifications for these twelve responses are outlined. Criteria for complete remission are A1, B1, C1, and D1; for partial remission A1 or 2, B1 or 2, C1 or 2, and D1 or 2; and for clinical remission D1 or 2. Complete remission is considered terminated (relapse) when: (a) the number of leukemic cells in marrow increases 20 per cent or more, or the total number of leukemic cells and lymphocytes exceeds 50 per cent; (b) leukemic cells in peripheral blood are in excess of 10 per cent of the differential count, or the total number of leukemic cells and lymphocytes exceeds 70 per cent; (c) there is definite evidence of leukemic infiltration; and (d) symptoms definitely ascribable to leukemia appear.

Bisel, H. F.: Criteria for the evaluation of response to treatment in acute leukemia. [Letter to the Editor.] Blood 11:676-677, July, 1956.

Treatment of Malignant Lymphomas

Histologically the malignant lymphomas are classified into (1) lymphosarcoma, including giant follicular lymphoma, lymphocytic and lymphoblastic lymphosarcoma, and reticulum-cell sarcoma, and (2) Hodgkin's disease, including paragranuloma, granuloma, and sar-

coma. There may be transition from one type to another or coexistence of different types in the same patient. Giant follicular lymphoma is usually relatively benign and is radiosensitive. Reticulum-cell sarcoma is malignantly progressive and therapeutically nonresponsive. Hodgkin's sarcoma has a similar clinical picture. Hodgkin's granuloma, the "classic" clinical form of the disease, is particularly susceptible to the palliative effects of the nitrogen mustards. Hodgkin's paragranuloma is relatively localized and only latently troublesome. Choice of treatment depends upon the clinical extent of the disease at the time of diagnosis. All unaccountably enlarged lymph nodes should be biopsied. Localized lesions are removed surgically or treated with roentgen irradiation. In disseminated lymphoma treatment is directed to relief of symptoms and control of particularly troublesome foci of disease. Roentgen irradiation and chemotherapy with nitrogen mustards, TEM, TEPA, thio-TEPA, ACTH, and cortisone are palliative measures but there is no cure for disseminated malignant lymphomas.

Cooper, T., and Childs, D. S., Jr.: Current status of treatment for malignant lymphomas. M. Clin. North America 40:1133-1140, July, 1956.

Acute Leukemia—Treatment

Previous to 1947, when aminopterin was developed, management of acute leukemia consisted solely of transfusions, followed by dismissal from the hospital with prediction of death within a few weeks or months, usually from massive hemorrhage or infection. Spontaneous remissions of eight to ten weeks occurred in from 1 to 10 per cent of children with acute leukemia. With the availability of the folic acid antagonists—aminopterin and amethopterin (methotrexate), the hormones — ACTH and corticosteroids, and the antipurines — as 6-mercaptopurine, remissions of greater frequency and duration are obtained. In the experience of the author with 700 children over the first nine years, 50 per cent of the patients survived for nine months under treatment with folic acid antagonists, ten months when ACTH or corticosteroids were added, and eleven months since 6-mercaptopurine can be employed either initially or subsequently to loss of response to the earlier substances. Ten per cent of the children now survive for twenty-seven and one-half months. One patient under constant treatment with folic acid antagonists has been in remission for six years and three months without toxicity or ill effect upon growth or development. Adults respond to 6-mercaptopurine better than to the antifolic compounds. The cytotoxic agents, the nitrogen mustards, Haddow's phenylbutyric mustard, the ethyleneimines, the carbamates, and the antibiotics, although not active in acute leukemia, have favorable effects in some forms of chronic leukemia, lymphoma, and Hodgkin's disease. If development of resistance to these antileukemic agents could be overcome, their use in acute leukemia would be analogous to that of insulin in diabetes and of liver products in pernicious anemia, bringing not only increased survival but a full life span to the patient and greater comfort and happiness to him and his family. The author predicts that the cure for leukemia will be found long before its exact nature or cause.

Farber, S.: The treatment of acute leukemia. [Editorial.] J. Chron. Dis. 3:455-457, April, 1956.

Leukemias—Classification and Treatment

From a twenty-four-year experience with 273 cases of leukemia the author gains the impression that, since the frequency of the chronic leukemias remains substantially unchanged and acute leukemia is progressively increasing in frequency, the acute type may be caused by an infectious agent that disperses, but that probably requires an individual susceptibility to manifest itself. The treatment of the leukemias has almost reached the same state as that of diabetes and pernicious anemia. The hormones and antimetabolites used in therapy, although not curative, often give the patient a nearly normal

life for additional months and years. In the treatment of acute hemocytoblastic leukemia without hemorrhagic diathesis, aminopterin is the author's choice. ACTH and cortisone should be used in acute hemocytoblastic leukemia together with aminopterin, or, in presence of hemorrhagic symptoms, without it. Resistance to both these substances eventually develops. TEM and radioactive phosphorus are inefficient in the acute leukemias. In the chronic leukemias radioactive phosphorus gave no better results than did roentgentherapy. Urethane and Fowler's solution give good temporary results but have serious inconveniences. TEM is the present preferred drug for chronic myeloid and lymphoid leukemia. It assures the patient a practically normal life, without restrictions in the manner of living.

Rosenfeld, G.: Considerations on the classification frequence and treatment of leukemia. Acta Unio internat. contra cancrum 11:313-317, 1955.

Leukemia in American Physicians

In the general population of the United States 4.3 per cent of cancer deaths are from leukemia. In infancy 60 per cent of all cancers are leukemias, and 40 to 50 per cent in the following fourteen years. Between the ages 15 to 29, 20 per cent of fatal cancer cases are leukemia. After age 30 the leukemia ratio drops rapidly to 2 or 3 per cent. On account of their age, physicians dying of cancer should have a leukemia ratio of less than 4.3 per cent; but the actual ratio is 8.3 per cent. The ratio of leukemia deaths to the total of all deaths in physicians is 1.2 per cent, and the corresponding figure for white males in the general American population is 0.54 per cent. In all age groups physicians have excessive ratios of leukemia whether compared to general mortality or to cancer mortality; and in radiologists, the ratios are 6 times higher than in the total of physicians. The ratio of leukemia to all cancers diminishes with age proportionally less among physicians than in the general male population, showing continuously augmented professional damage to the hemopoietic organs. The latency period of professional leukemia is short. The danger of leukemia increases with the increased use of fluoroscopy. Protective aprons and gloves should be used more effectively.

Peller, S., and Pick, P.: Leukemia in American physicians. Acta Unio internat. contra cancrum 11:292-294, 1955.

Fresh Blood in Leukemia

The leukocyte count falls with significantly greater frequency in leukemic patients transfused with fresh blood than with stored blood, suggesting that the blood of normal individuals may contain an antileukemic factor which is absent from the blood of leukemic individuals. There was no evidence, from seventy-seven transfusions in twenty-three patients, that either fresh or stored blood gave complete or partial remission or in any way modified the differential leukocyte count. Perhaps the defect in leukemia is not an intrinsic, immutable abnormality of the leukemic cells themselves, but rather a failure of some humoral regulating mechanism which could be correctable by replacement therapy.

Wetherley-Mein, G., and Cotton, D. G.: Fresh blood transfusion in leukemia. Brit. J. Haemat. 2:25-31, Jan., 1956.

Acute Leukemia in Adults

By the simultaneous use of full dosages of 6-mercaptopurine and ACTH or cortisone four of five adults with acute leukemia had complete clinical remissions. Four patients had a total of thirteen complete, satisfactory, or incomplete hematologic remissions. The remissions were more sustained than would be expected from 6-mercaptopurine, ACTH, or cortisone alone. Three patients lived for ten, seventeen, and twenty months respectively after the diagnosis was made. Treatment was not discontinued in any case because of toxic effects. The daily dosages used were: 6-mercaptopurine 2.5 mg. per Kg. orally, ACTH 120 units intramuscularly, and cortisone 300 mg. orally.

Moynihan, J. W., and Berman, L.: Acute leukemia in adults; treatment with the combined use of ACTH or cortisone and 6-mercaptopurine. J. Michigan M. Soc. 55:309-314, March, 1956.

Etiology of Leukemia

Arthur Kirschbaum, M.D.

Leukemia is a disease characterized by overproduction of white blood cells, usually of a specific type. *Human leukemia* can be associated with no known infectious agent which initiates the abnormal hemopoietic activity.

In acute leukemia extremely immature cells are present in the circulating blood. These abnormal cells infiltrate the various organs in which they multiply, but the cellular accumulations are not as great as in *chronic leukemia*. The chronic disease is usually either *lymphocytic* or *granulocytic;* this classification is based on the differentiation of the most immature leukemic cells to either lymphocytes or granulocytes.

Survival is measured in weeks or months in acute leukemia, months or years in the chronic disease. Chronic leukemia is rare in children; acute leukemia is found less commonly than chronic leukemia in adults. Some investigators question the grouping together of acute and chronic leukemia as one disease, pointing out that acute leukemia of childhood is associated with serious infection, hemorrhage early in the disease, and with less cellular infiltration of liver, spleen, and lymph nodes. The response of the chronic and acute leukemias to chemotherapeutic agents and ionizing irradiation differs—the folic acid antagonists (aminopterin, amethopterin) altering the course of acute but not chronic leukemia, roentgen rays effecting a more favorable response in the chronic disease, rarely if ever being used to control acute leukemia.

Lymphosarcoma, multiple myeloma, chloroma, and Hodgkin's disease are hemopoietic cellular overgrowths generally considered to be frankly neoplastic. Similarities between these diseases and leukemia have influenced many workers to regard all as different morphological manifestations of one basic disease.

Although leukemia was recognized as a clinical entity more than 100 years ago, most of the investigative effort was descriptive until 1908 when Ellerman and Bang, working on leukemia in the domestic fowl, found that this disease can be transmitted to certain susceptible chickens by the inoculation of either leukemic cells, cell-free extracts, or cell-free filtrates derived from leukemic blood plasma. Ellerman and Bang postulated that chicken leukemia is a virus disease.

The first experimental study in mammals appeared in 1927 when Snijders and Tio Tjan Gie described leukemia and lymphosarcoma in a genetically homogeneous stock of guinea pigs. Guinea-pig leukemia, unlike chicken leukemia, could be transmitted to closely related young adult animals only by the inoculation of intact viable cells, and not by cell-free tissue extracts. Introduced cells (derived from either leukemic tissue or blood) grew at the site of inoculation to form tumors. When cells of the local tumors were suspended in saline and inoculated intravenously into closely related animals, the recipients developed leukemia.

In 1929 Richter and MacDowell described leukemia in an inbred strain of mice, mated in successive generations brother-to-sister. Although 90 per cent of the animals of this genetically homogeneous stock developed spontaneous leukemia, approximately 10 per cent remained leukemia-free. Ninety per cent of the progeny of nonleukemics developed leukemia, indicating that the 10 per cent nonleukemics were probably genetically similar to the 90 per cent in which the disease appeared. It was assumed, therefore, that non-genetic factors were responsible for the non-appearance of leukemia.

The next most important step in the study of the pathogenesis of mouse leu-

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kemia was the observation by Furth that leukemia may be induced in low-leukemia strains of mice by exposure to roentgen rays. This was the first experimental demonstration that leukemia may be induced in animals which otherwise remain leukemia-free.

Atomic bomb casualties in Hiroshima have developed more leukemia than the non-irradiated Japanese population, indicating that in the human species as well, ionizing radiations may be leukemogenic. Earlier investigations indicated that the incidence of leukemia is higher in physicians than in the remainder of the population, and higher in radiologic than in non-radiologic doctors. Heavy irradiation of human subjects with roentgen rays administered therapeutically has also been associated with the subsequent development of leukemia.

Morton and Mider in 1939 showed that the carcinogenic hydrocarbons that had been used to induce local skin tumors by direct application induce leukemia in certain genetically susceptible strains of mice. This has been interpreted as evidence that mouse leukemia is a neoplasm, chemicals inducing obvious cancers also causing the appearance of leukemia.

A third class of agent, estrogenic hormones, was discovered by Lacassagne in France to be leukemogenic. This finding is difficult to reconcile with the possible etiology of the disease in man. Since related steroids (glucocorticoids) of the adrenal cortex may modify the progression of leukemia in humans, there may be some fundamental link between the induction of leukemia in mice by estrogenic hormone and the occurrence of the disease in man. In high-leukemia strains of mice the periodic administration of large doses of cortisone (monthly intervals) significantly delays the onset of lymphocytic leukemia, although the ultimate incidence is the same as in untreated controls. Androgenic hormone also delays the development of lymphocytic leukemia in castrated males, in which the onset of leukemia is accelerated by removal of the testes. The development of lymphocytic leukemia occurs earlier in females and the total incidence tends to be higher than in the males of selected mouse populations.

Contrary to the observations on lymphocytic leukemia, roentgen-ray induced granulocytic leukemia occurs more frequently in males than females and gonadectomy reduces the incidence in males (Upton and Furth). This greater susceptibility of males to granulocytic leukemia, with the converse true for the lymphocytic variety of the mouse disease, might explain the discrepancy between sex incidence in mice and man. In mice, although more leukemia is found in females, the usual type is lymphocytic. In man leukemia is found more commonly in males, especially in the older age groups where the granulocytic variety predominates.

In 1950 Gross reported and later Woolley confirmed the induction of leukemia in low-leukemia mice by the inoculation of newborns with cell-free leukemic tissue (mouse) extracts. Gross's interpretation of his results has been that the low-leukemia mice lack an agent which can cause leukemia to appear if it is introduced into mice either at birth or within a very few hours thereafter. The agent must be extracted by special procedures, and inoculated mice may develop not only leukemia but fibrosarcomas of the skin or tumors of the parotid gland. High-leukemia strains develop leukemia earlier than otherwise (Latarjet, Lacassagne, Dulaney) if they are inoculated at birth with leukemia extracts. Graffi has reported the induction of leukemia in mice injected as newborns with extracts of the Ehrlich ascites tumor, suggesting that non-leukemic cells might harbor the agent.

Since extracts derived from the embryos of high-leukemia strains have been found by Gross to have leukemia-inciting activity (when injected into newborns of low-leukemia strains), the agent has been considered to be present prior to the development of leukemia in these stocks, and to be transmitted by the germ cells. Frankly leukemic cells are usually not present in high-leukemia strains prior to 6 months of age (Furth) as determined by transplantation studies. The virus, according to Gross's investigations, induces transforma-

tion of normal cells to leukemic cells.

Certain important questions relating to viral etiology remain unanswered. In the first place, is the "virus" comparable to the agents responsible for the infectious diseases such as measles and chicken pox? Second, how can one account for the "spontaneous" cases of leukemia which occur even in "low-leukemia" stocks of mice? These cases occurring sporadically are actually more similar to human leukemia than those occurring in "high-leukemia" populations where genetic factors are potent in determining leukemogenesis. Third, how does a virus relate to the induction of leukemia in "low-leukemia" strains of mice by agents such as carcinogenic chemicals and roentgen rays, which are administered weeks or months after birth? Are these agents independently leukemia-inciting, or is their action mediated by a leukemia virus?

Furth has found that the leukemias developing in mice inoculated with leukemic tissue extracts at birth are not always of the genetic type of the recipient, but are genetically of the donor type. If cells were not transplanted at the time of newborn inoculation, then chromosomal materials (DNA, deoxyribosenucleic acid) extracted from the leukemic cells may have transformed cells of the new-born recipient so that they now possessed the acquired potential to develop leukemia. This implies that the "virus" of Gross might be an integral part of the chromosomes which causes the cells to become leukemic. It would be transmitted via cell division, and thus to progeny via germ cells normally, or artificially by cellular extraction and inoculation into newborn mice.

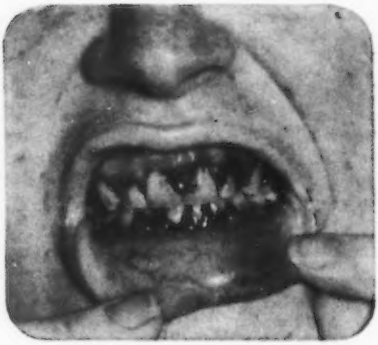
"Spontaneous" leukemias occurring in "low-leukemia" stocks are not explainable on the basis of "viral" induction, unless these strains are not completely "virus-free." With a small amount of virus the disease might become manifest late in life. Whether these spontaneous leukemias possess the "leukemia agent" will be an important area of investigation.

The leukemias induced by roentgen rays and carcinogenic chemicals might be unrelated to viral action. *Multiple factors* are capable of contributing to the induction of leukemia, some of these by their independent action. Leukemia appears in mice of certain strains when carcinogenic chemicals, estrogenic hormones, or roentgen rays are given alone. Their action may be additive; when given together leukemia may appear earlier and more frequently. Agents which are not independently leukemia-inciting may augment leukemogenesis. It has been found in our laboratories that urethane, a chemical which "independently" induces lung tumors, but not leukemia, in mice, remarkably augments the leukemia-inciting activity of roentgen rays. If *multiple factors* are necessary for the expression of leukemia, and if co-leukemogens (augmenting factors) operate which are not independently leukemogenic, the problem is indeed complex, for promoting factors (co-leukemogens) might be exceedingly difficult to detect.

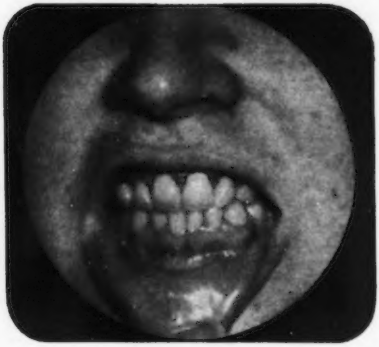
Of potential significance to a more complete understanding of leukemogenesis are the observations of Schwartz. Mice of high-leukemia strains developed leukemia earlier than controls if inoculated with extracts of either human or mouse leukemic brains. Mice inoculated with extracts of normal brains developed leukemia at the expected time. The work suggests an "accelerating" filterable agent which does not independently cause the development of leukemia. Work on mouse mammary cancer (Heston, Muhlbock) suggests that the virus associated with this disease is not an essential etiologic agent, but a strong "promoter" or "accelerator" of other factors. It is possible that for leukemia, too, there are agents which operate in the absence of a virus, but whose leukemia-inciting properties are potentiated by a filterable viral agent.

Certain lymphoid tissue of a mouse may be more susceptible than the remaining lymphoid tissue to the induction of lymphocytic neoplastic (leukemic) change. Kaplan found that although a particular strain of mouse was susceptible to the induction of leukemia by roentgen rays, removal of the thymus prior to roentgen

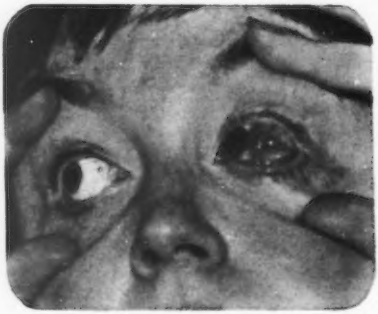
(Continued on page 56)



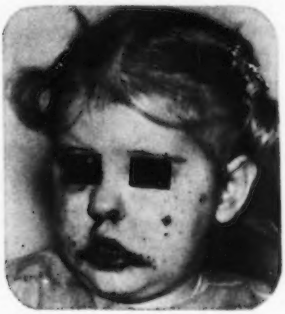
1. C.M. Acute leukemia in a 33-year-old woman with hyperplastic gingivae and oral ulcers—before treatment.



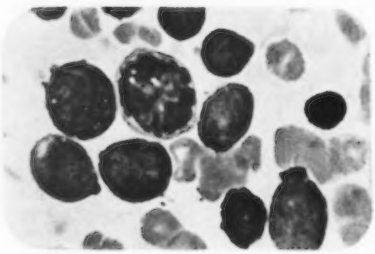
2. C.M. Complete clinical response to 6-MP and cortisone and partial hematological response in marrow and peripheral blood, one month later.



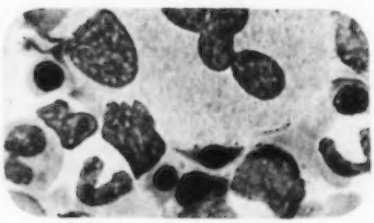
3. C.M. Leukemic infiltration of eyes denoting relapse accompanied by anemia, thrombocytopenia, rapidly rising leukocyte count; patient died of septicemia nine months after onset of disease.



4. B.L. Acute leukemia in 2-year-old girl showing relapse after eight months' remission; patient died two months later.



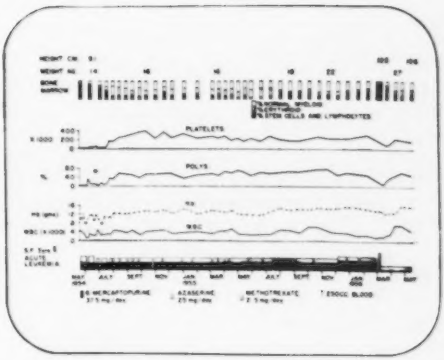
5. W.C. Acute leukemia in 6-year-old boy showing completely -blastic marrow before treatment.



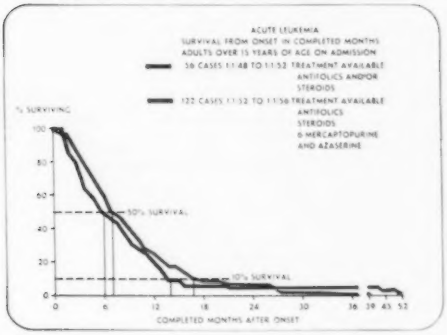
6. W.C. Normal hematopoiesis with presence of erythroid activity and mature granulocytes and megakaryocytes in marrow of patient in remission after course of treatment with 6-MP and azaserine.

ILDREN AND ADULTS

7. S.F. Five-year-old girl with acute leukemia during a one and a half year remission on 6-MP and azaserine.

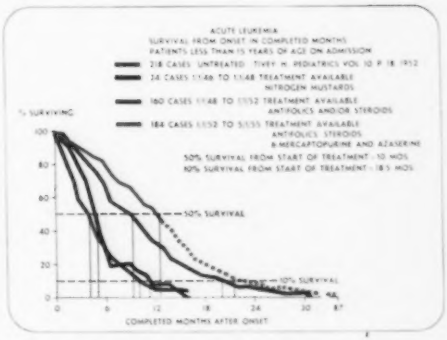


8. S.F. Course of disease during treatment.



9. Survival in adult patients with acute leukemia treated with available chemotherapeutic agents.

10. Survival in children with acute leukemia; 50 per cent survive twelve months with chemotherapeutic agents now available.



Courtesy of Doctors J. H. Burchenal, R. R. Ellison, M. L. Murphy, and T. C. Tan, Division of Clinical Chemotherapy, Sloan-Kettering Institute, and Departments of Medicine and Pediatrics, Memorial Center for Cancer and Allied Diseases, New York City.

irradiation prevented the induction of leukemia. When thymus (of the same inbred strain) was transplanted to thymectomized mice after irradiation (thymus unirradiated) leukemia was induced. Since the thymus *per se* was not irradiated, the effect of irradiation was indirect, that is, a factor resulting from irradiation was formed in the tissues and this factor acted preferentially on the thymus, even if the latter had not been irradiated. Thymus from mice of only specific genetic constitution is subject to the indirect leukemogenic effects of roentgen irradiation. Transplantation studies indicate that the "genetic" factors controlling "susceptibility" operate in the target tissue itself, and that thymus of "high-leukemia" strains is far more susceptible to leukemogenic factors than lymph nodes or spleen. Thymectomy reduces the incidence of spontaneous leukemia in high-leukemia stocks (Furth), and removal of the thymus has decreased susceptibility to the induction of leukemia by carcinogenic chemicals (Law). Law has demonstrated by carefully designed experiment that thymic tissue of high-leukemia strains induces the leukemic transformation of lymphocytes invading it. In other words, thymic tissue of high-leukemia strains not only possesses *cells* which are likely to undergo leukemic transformation, but the *thymic environment* is most suitable for the alteration of the lymphocyte from normal to leukemic.

Additional points of significance in the etiology and pathogenesis of leukemia in experimental animals are the following: "Genetic" susceptibility may apply to only one type of leukemogenic stimulus. For example, a strain of inbred mice susceptible to the induction of leukemia by roentgen rays may resist the leukemogenic action of a carcinogenic chemical (methylcholanthrene). Age is a factor of importance determining susceptibility, younger mice of a "genetically susceptible" group being more susceptible to specific leukemogenic stimuli than older mice which are, however, genetically identical. Nutritional factors are important, optimum nutrition favoring the induction of leukemia in mice. When mice susceptible to the induction of leukemia by roentgen rays are given transfusions of bone marrow from genetically similar mice, protection is afforded against the induction of leukemia. Similar bone-marrow treatment protects against the lethal effects of roentgen rays.

Certain factors have been considered of probable significance in human leukemogenesis. From the studies of the Atomic Bomb Casualty Commission in Japan there can be no doubt that ionizing radiation can induce leukemia in man. It has been suggested that leukemia as a terminal manifestation of polycythemia vera may be the result of the radiation therapy given these patients (Schwartz and Ehrlich). Benzol has been indicted as a leukemogenic industrial hazard, but controlled studies on animals have not as yet supported this contention. Leukemia has appeared in twins and in siblings indicating the importance in certain instances of genetic factors. Genetic factors might operate in determining susceptibility to extrinsic agents (e.g., ionizing radiation), not all similarly exposed individuals becoming leukemic. Congenital leukemia is very rare, and the offspring of mothers leukemic during pregnancy may remain free of the disease. Although infections are associated with leukemia, there is no evidence of any causal relationship.

Although the etiology of most leukemias still remains unknown, the experimental results in animals will probably be very significant for our understanding of the pathogenesis of human leukemia. At least one agent (ionizing radiation) may cause leukemia to appear in both mouse and man. Similarity of response of mouse and human leukemia to therapeutic agents (Burchenal) reinforces the feeling that knowledge gained from studies on the pathogenesis and etiology of animal leukemia will be significant for the human disease.

Chemotherapy of Leukemia

Rose Ruth Ellison, M.D., and Joseph H. Burchenal, M.D.

The chemotherapy of leukemia has made great progress since Lissauer in 1865 described benefit from the use of arsenic in the treatment of two cases of chronic leukemia. Although radiation remains the most used therapy for the chronic leukemias, most recent progress has been made in chemotherapy. Some of the real advances in this discipline, however, lie in the theoretical realm rather than in practical therapy.

Neither radiation nor presently available chemotherapy is curative of any type of leukemia. The clinician can, however, prolong the lives of many patients with acute leukemia, and in the chronic forms at least the useful and perhaps even the actual survival time of the patient can be increased. Agents available for the chemotherapy of the leukemias are as follows:

I. Acute Leukemia
- A. Antimetabolites
  - 1. Antagonists of folic acid
    - a. 4-Amino derivatives of pteroylglutamic acid
    - b. Diamino-dichlorophenyl pyrimidines
    - c. Dihydro-triazines
  - 2. Antagonists of purines
    - a. 6-Mercaptopurine
    - b. Thioguanine (6-mercapto-2-amino-purine)
    - c. 6-Chloropurine
  - 3. *o*-Diazoacetyl-L-serine
- B. Hormones
  - 1. ACTH
  - 2. Cortisone
  - 3. Hydrocortisone
  - 4. Meticorten

II. Chronic Myelocytic Leukemia
- A. Polyfunctional Alkylating Agents
  - 1. Nitrogen mustard
  - 2. Triethylenemelamine
  - 3. Triethylenephosphoramide
  - 4. Triethylenethiophosphoramide
  - 5. Myleran
  - 6. 1,3-Bis(ethyleneimino-sulfonyl)propane (BEP)
- B. General Cell Poisons
  - 1. Urethane
  - 2. Arsenic
  - 3. Benzol
  - 4. Demecolcin
- C. Antimetabolites
  - 1. Purine Antagonists
    - a. 6-Mercaptopurine
    - b. Thioguanine
    - c. 6-Chloropurine

III. Chronic Lymphocytic Leukemia
- A. Polyfunctional Alkylating Agents
  - 1. Nitrogen mustard
  - 2. Triethylenemelamine
  - 3. Triethylenephosphoramide
  - 4. Triethylenethiophosphoramide
  - 5. Chlorambucil
- B. General Cell Poisons
  - 1. Urethane
- C. Hormones
  - 1. Cortisone
  - 2. Hydrocortisone
  - 3. Meticorten
  - 4. ACTH

I. ACUTE LEUKEMIA

Adrenal steroids, ACTH, and certain antimetabolites are of value in the management of acute leukemia.

The folic acid antagonists were first shown to be of benefit in acute leukemia by Farber, *et al.*,[9] in 1948. Aminopterin and methotrexate (amethopterin), which are the 4-amino substituted derivatives of pteroylglutamic acid, are the most useful. They are almost always given orally. The average dose for a 5-year-old child is 0.25 to 0.5 mg. of aminopterin and 2.5 to 5.0 mg. of methotrexate. (Since there is

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approximately a tenfold difference in the dosage of these two drugs, it is important to differentiate between the two.) Caution should be used in treating patients with impaired renal function since in this situation considerable amounts of the antagonist will remain in the serum for prolonged periods after administration.[4] At the usual therapeutic dosage, at least the initial remission can usually be obtained in children with normal renal function without the development of toxicity. Eventually the leukemic cells develop resistance to the antagonists, and it becomes necessary to increase the dose to the point where mild toxic signs appear. If toxicity occurs, treatment is discontinued temporarily and is then resumed after the signs subside and continued until a remission is achieved. If treatment at these dosage levels is interrupted at the time of the first toxic manifestations (anorexia, ulceration of the oral mucosa, and mild gastrointestinal disturbances) more severe disturbances will not follow.

It may take as long as eight weeks to obtain a remission. The average length of such remissions is approximately eight months, varying in individual instances from one month to over two years. Good clinical and hematologic remissions occur in 30 to 50 per cent of the children treated with the folic acid antagonists but are rare in adults so treated.[5]

The purine antagonists, another type of antimetabolite useful in the treatment of leukemia, have been studied more recently. 6-Mercaptopurine is the most widely used of this group.[6] It is given orally with a daily dose of 2.5 mg./Kg. of body weight and from three to twelve weeks may be necessary for beneficial effects to be noted. At this dosage level, toxic effects in children are rare, other than a fall in leukocyte count. Anorexia, nausea, and vomiting occasionally occur in adults.

6-Mercaptopurine produces remissions in approximately one-third of the children and one-seventh of the adults so treated.[2] The remissions in children occur in those whose disease is resistant to methotrexate and cortisone as well as in previously untreated patients with acute leukemia.

Since at least three weeks may elapse before beneficial effects result from the use of the folic acid antagonists or 6-mercaptopurine, adrenal steroids and ACTH are the drugs of choice when rapidity of action is necessary (i.e., in serious bleeding or rapid deterioration of the patient).[10, 23] The usual dosages are: cortisone, 100 mg. (children) to 300 mg. (adults) daily orally; hydrocortisone, two-thirds of this dose orally or intravenously; meticorten, 50 to 100 mg. daily orally; and ACTH, given as a constant intravenous drip at 25 to 50 mg. per 24 hours or the gel intramuscularly once or twice daily at 100 mg. a day.

Remissions are induced by ACTH and the steroids in 50 to 70 per cent of the children and 25 per cent of the young adults treated but are of relatively short duration.

Since the development of resistance influences profoundly the results obtained in the chemotherapy of leukemia, many investigators connected with the fields of genetics, biochemistry, and the chemotherapy of infectious disease feel that combination therapy with two or more agents might well prevent the development of this resistance and answer the therapeutic problem of leukemia. To date, combinations of methotrexate and cortisone, 6-mercaptopurine and methotrexate, and methotrexate and azathymine given to patients with acute leukemia have shown no increased benefits. Another compound, *o*-diazoacetyl-L-serine (azaserine), was of no practical value in treating leukemia[7] when given alone. When a selected group of children with acute leukemia was treated with the combination of azaserine and 6-mercaptopurine, however, there appeared to be an increase in the incidence and duration of remissions.[3] This combination is being studied further.

In planning the treatment of patients with acute leukemia, certain factors about the three classes of agents available must be taken into account. (1) The purine antagonists and the folic acid antagonists cause longer and more satisfactory remissions than ACTH and the steroids, but

take from three to twelve weeks to exert their beneficial effects. (2) The adrenal steroids and ACTH act much more rapidly than the antimetabolites but the remissions are of relatively short duration. (3) The folic acid antagonists rarely have beneficial effect in adult patients. (4) There is no cross resistance among the three different classes of agents.

The acutely ill patient should therefore be started on adrenal steroids or ACTH. Once the patient has been brought into remission or tided over the acute emergency, antimetabolite therapy should be started. Antimetabolites should also be employed for the patients appearing in relatively good condition initially, using methotrexate or 6-mercaptopurine or 6-mercaptopurine plus azaserine for children and 6-mercaptopurine for adults. Thrombocytopenia and leukopenia before treatment are not contraindications to antimetabolite therapy.

It would appear that the addition of 6-mercaptopurine and azaserine to the agents previously available has increased the survival time of children with acute leukemia. In adults, the percentage of remissions that can be achieved with all these different agents is much lower and any increased longevity which may be achieved in the remitting patients is not significantly reflected in the over-all survival time statistics.

II. CHRONIC GRANULOCYTIC LEUKEMIA

There are many forms of therapy useful in early chronic granulocytic leukemia. In this form of leukemia, in contrast to acute leukemia, resistance to one therapeutic agent generally means resistance to all, since the patient is usually then in the acute terminal stage of the disease. Radiation therapy either by localized roentgen ray, total-body–spray irradiation, or P^{32} is probably the most widely employed form of therapy. Several of the chemotherapeutic agents, however, are equally satisfactory. Of the chemotherapeutic agents presently available, arsenic was the first to be employed.[19] It is given by mouth in the form of Fowler's solution, starting at 5 minims 3 times daily and increasing 1 minim daily to the maximum tolerated dose, which may be as high as 20 minims 3 times daily. The administration of this drug often causes nausea and vomiting but, if tolerated, it will produce satisfactory remission.

Urethane[21] can produce beneficial results in patients with chronic granulocytic leukemia. Two to 4 gm. orally, daily, induces remissions in a high percentage of these cases but administration has to be continued over long periods of time, and nausea and vomiting are annoying side effects, frequently severe enough to make continued administration impossible.

The nitrogen mustard, methyl-bis(beta-chloroethyl) amine (HN2), was the first of the polyfunctional alkylating agents to be used in the treatment of this disease. It must be given intravenously with a course of treatment consisting of 0.4 mg./Kg. of body weight given either as a single dose or in four daily doses of 0.1 mg./Kg. each.

Nausea and vomiting commonly follow administration of the drug but last for only 24 hours and are not a contraindication to further therapy. Remissions last from one to six months with such a course of therapy, and may be repeated.[13, 16, 18]

Another polyfunctional alkylating agent, triethylenemelamine (TEM),[17] can be taken orally and causes little nausea and vomiting. It can therefore be given on an outpatient basis and as maintenance therapy. The usual dose of TEM in this form of the disease is 5 mg. one hour before breakfast, on two consecutive days each week, until such time as the white count has reached normal levels. Maintenance therapy is then adjusted in an attempt to keep the white count below 20,000.

Newer agents being studied for their effects on chronic granulocytic leukemia include 6-mercaptopurine and Demecolcin, as well as several polyfunctional alkylating agents including myleran (1,4-dimethanesulfonyloxybutane), TEPA (triethylene phosphoramide), thio-TEPA (triethylene thiophosphoramide), and BEP

(1,3-bis (ethyleneimino-sulfonyl) propane).

Myleran [12, 14, 15] was found to have a marked depressive effect on the myeloid series both in the rat and in man. Clinical studies indicate myleran to be very useful in the control of chronic myelocytic leukemia. Important limiting side effects are thrombocytopenia and agranulocytosis, but these are unlikely to be serious if large doses are avoided and if treatment is withheld when the platelet count is below 100,000 per cubic millimeter. The suggested course of therapy is a daily dose of 4 to 10 mg. orally for several weeks until response has occurred, followed by a smaller maintenance dose.

Another agent similar in effect to myleran in that the granulocyte depression is much more marked than the lymphocyte depression is 1,3-bis(ethyleneimino-sulfonyl) propane (BEP).[22] BEP has produced remissions in chronic granulocytic leukemia.

Two other compounds with nitrogen-mustard-like activity, are TEPA[8, 25] and thio-TEPA.[24] These affect lymphocytes as well as granulocytes. Both compounds have led to good clinical and hematologic responses in chronic granulocytic leukemia but are not superior either to TEM or myleran.

Demecolcin[20] (deacetyl methyl colchicine) differs from the above group of compounds in that it is classified as a general cell poison. Its antimitotic action is similar to that of colchicine in normal and malignant cells in tissue culture, but the general toxicity of demecolcin is much less than that of colchicine. Patients with chronic granulocytic leukemia treated with demecolcin, 3 to 7 mg. daily, showed good hematologic and clinical responses. Continued therapy with a maintenance dose is necessary to prevent rapid relapse. There are no subjective side effects with the doses used. Inhibition of spermatogenesis and slight alopecia have been caused by demecolcin.

6-Mercaptopurine has also produced good responses in most of the earlier cases of chronic granulocytic leukemia as well as in a few in the blastic phase. The data are not yet available on the long-term effect of using the antipurines as the initial therapy in this disease but several patients have been treated continuously for periods ranging from two to four years successfully.

The usual dose of 6-mercaptopurine in this disease, as in acute leukemia, is 2.5 mg./Kg. daily and a maintenance dose at the full therapeutic level is usually necessary to prevent relapse within six weeks. Anemia and thrombocytopenia have occasionally developed in these patients after prolonged use of 6-mercaptopurine. This has been reversible, clearing when the drug was discontinued temporarily.

To summarize the current status of chemotherapy in the treatment of chronic granulocytic leukemia: Myleran, TEM, urethane, HN2, and arsenic, in order of preference, are useful agents. TEPA and thio-TEPA do not seem to offer anything more than does TEM, either in ease of administration or in results obtained. Demecolcin seems to rank with the polyfunctional alkylating agents and with urethane, but more study of this drug is necessary. 6-Mercaptopurine is effective both in the early and later stages of the disease but whether it should be used in the early stages or be reserved for use in the terminal -blastic stage is not clear at present.

III. CHRONIC LYMPHOCYTIC LEUKEMIA

A long asymptomatic period may follow the onset of this disease and the patient should be managed conservatively. During this time, treatment should not be given just for the elevation of the leukocyte level, but should be reserved for the development of bulky, uncomfortable adenopathy, hepatosplenomegaly, or systemic evidence of disease. The local disease is probably best treated by small doses of roentgen ray to the involved area or by P^{32}. When the adenopathy becomes widespread or marrow involvement is evident, the addition of chemotherapeutic agents may be helpful.

In chronic lymphocytic leukemia ar-

senic, 6-mercaptopurine and Demecolcin have not proven useful, causing only leukocyte depression without clinical improvement. Urethane is much less effective than in chronic myelocytic leukemia. With the polyfunctional alkylating agents TEM, HN2, TEPA, and thio-TEPA, good clinical response can be achieved, with TEM appearing to be the most convenient agent among these.

Patients with chronic lymphocytic leukemia seem to be more sensitive to these agents than are patients with chronic granulocytic leukemia, and the drugs must therefore be given cautiously. In chronic lymphocytic leukemia the initial dose of TEM is a single one of 2.5 mg. orally. Further therapy is not given, once the leukocyte count begins to fall, until it stabilizes. The development of anemia and thrombocytopenia while receiving an adequate amount of TEM is an indication for stopping treatment.

Still another polyfunctional alkylating agent, chlorambucil (CB 1348) (p-bis(2-chloroethyl)aminophenylbutyric acid)[11] has more recently been found to inhibit particularly the lymphocytes of the peripheral blood of rats. Clinically it has proved of use in chronic lymphocytic leukemia and may have fewer side effects than the drugs previously mentioned. It is usually given orally at doses of 0.2 mg./Kg. daily until the leukocyte count is brought down to normal levels.[1, 20]

ACTH and the adrenal steroids are of value in the treatment of chronic lymphocytic leukemia, producing a decrease in adenopathy and hepatosplenomegaly and a rise in hemoglobin and platelet levels. Although the leukocyte count may also rise, this does not appear to be harmful. These drugs are especially useful in those patients with acquired hemolytic anemia secondary to chronic lymphocytic leukemia, and in those with thrombocytopenia. Patients often can be maintained on as little as 50 to 100 mg. of cortisone daily following a good response to a dose of 100 to 300 mg. daily.

The total care of the patient is particularly important in the treatment of leukemia. Specific therapy is only one aspect of the management of the patient. Massive doses of antibiotics should be employed whenever serious infections threaten the patient, but antibiotics should not routinely be given prophylactically, and transfusions should be given as often as necessary to combat anemia. Patients should be encouraged to lead as normal a life as possible within their physical abilities, in order to maintain morale.

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5:174, Sept., 1955	Cancer clinic.
6:136, July, 1956	Cancer clinic.

First Chemotherapy of Leukemia and Lymphomas

Lissauer (Berl. klin. Wchnschr. 2:403-404, 1865) reported good results in two cases of leukemia treated with Fowler's solution. The same preparation of arsenic had been used by Hodgkin in the treatment of his six patients with "morbid appearances of the absorbent glands" [Tr. Med.-Chir. Soc. London 17:68, 1832]. Arsenic today is still used as a general cell poison, like urethane, benzol, colchicine, and deacetyl methyl colchicine, in the treatment of chronic myelocytic leukemia.

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Etiology of Leukemia and Carcinoma

The "multifocal and autochthonous origin and the tendency to spontaneous remissions in leukemia distinguish it from tumours of epithelial origin and suggest that its aetiology may be fundamentally different."

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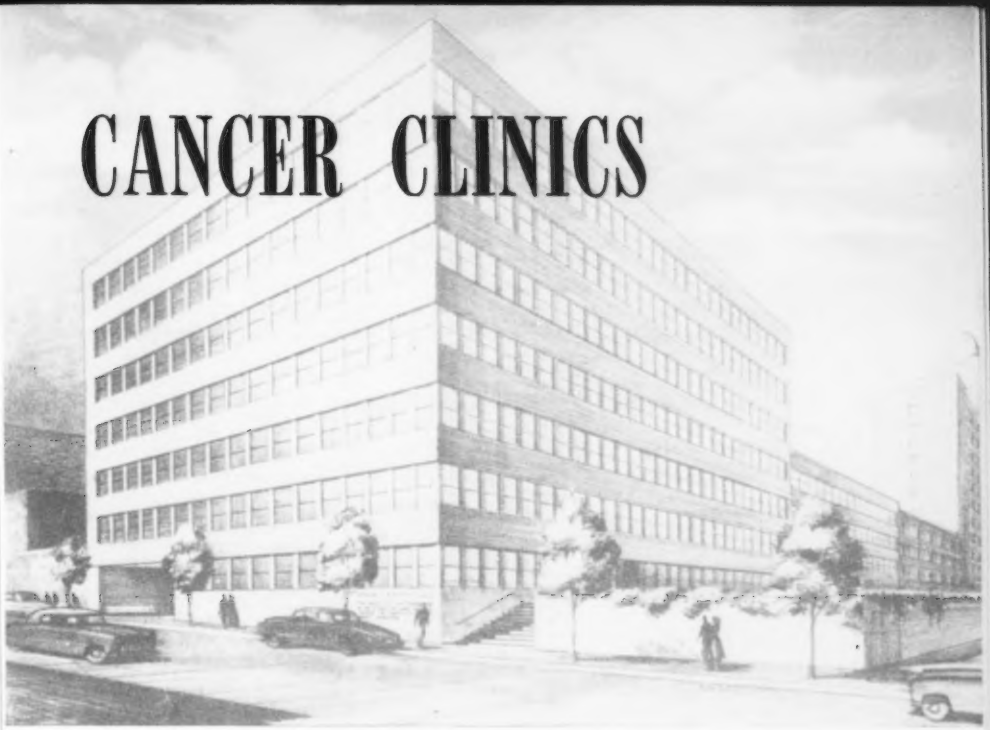
CANCER CLINICS



Diagnosis and Management of the Chronic Leukemias*

During the past decade or two all forms of leukemia have been reported with increasing frequency. This probably represents a true increase in the incidence of both the acute and chronic leukemias, particularly in the older age groups, rather than being merely a manifestation of better diagnostic facilities now available, or of the increased life span of the population.

Leukemia can be divided into acute and chronic forms depending upon the progress of the course of the disease, morphologically upon the immaturity and predominating type of cell seen, and upon associated systemic symptoms as well as anemia and thrombocytopenia. It is important to classify the leukemias as accurately as possible on the basis of the above criteria since the success of the selected therapeutic agent is to some extent dependent upon the accurate identification of the morphologic type of leukemia. Lists of drugs useful in the various leukemias and dosages are noted in Table I.

The insidious onset and course of any chronic leukemia is such that many months or years may elapse after the original diagnosis is suspected before a definite diagnosis is established. Although chronic granulocytic leukemia has a median survival of 3 to 3.5 years, individual cases vary greatly in their course, symptomatology, and survival. The recent use of the leukocyte alkaline phosphatase reaction has aided in the early differentiation of granulocytic leukemia from leukemoid reactions.

Synthesis of the opinions of the Staff of the Department of Hematology, The Mount Sinai Hospital, New York City, Dr. Louis R. Wasserman, Director: Attending Staff: Doctors Peter Vogel, Daniel Stats, Martin C. Rosenthal, Stanley L. Lee, Solomon Estren, Mary C. Tyson, Richard E. Rosenfield, Frank A. Bassen, Robert L. Rosenthal, Martin Sanders, Eugene A. Brody, and Celine R. Fletcher.

TABLE I. AGENTS USED IN THE TREATMENT OF THE LEUKEMIAS

Agent	Usual Dose*	Use
Purinethol (6-Mercaptopurine)	2.5 mg./Kg./day	Acute leukemia; chronic myelocytic leukemia
6-Chloropurine	20 mg./Kg./day	Acute leukemia
Aminopterin	0.5-1 mg./day	Acute leukemia
Methotrexate (Amethopterin)	2.5-5 mg./day	Acute leukemia
Busulfan (Myleran)	0.06 mg./Kg./day	Chronic myelocytic leukemia
Urethane (Ethyl carbamate)	1-3 Gm./day	Chronic myelocytic leukemia; chronic lymphocytic leukemia
Fowler's solution (Potassium arsenite)	15 drops/day increasing to tolerance	Chronic myelocytic leukemia
Triethylenemelamine (TEM)	1-5 mg. in divided doses	Chronic lymphocytic leukemia; chronic myelocytic leukemia
Nitrogen mustard (methyl-bis(β-chlorethyl)amine)	0.2-0.4 mg./Kg. in divided doses (intravenous)	Chronic lymphocytic leukemia; chronic myelocytic leukemia; "blast crisis"
Chlorambucil (CB 1348)	0.1-0.2 mg./Kg./day	Chronic lymphocytic leukemia
ACTH	50-100 mg./day (I.M. or I.V.)	Acute leukemia; chronic lymphocytic leukemia
Prednisone Hydrocortisone Cortisone	50-100 mg./day 100-300 mg./day; (100 mg./day I.V.) 100-300 mg./day	Acute leukemia in adults and children; Chronic lymphocytic leukemia
P^{32}	0.5-1 mc./wk. for total of 5 mc. (I.V.)	Chronic myelocytic leukemia; chronic lymphocytic leukemia
Roentgen ray	Dosage varies with site and disease	Chronic myelocytic leukemia; chronic lymphocytic leukemia

*Oral dose unless indicated.

Chronic granulocytic leukemia, comprising about 30 per cent of all cases of leukemia, is that form of leukemia most amenable to therapy during the greater part of its natural course. Hospitalization is rarely indicated early in the disease and ambulatory therapy is usually successful until the terminal phase. In most leukemias, complications such as anemia, marked bleeding tendency and severe infections necessitate close hospital observation and treatment. In chronic granulocytic leukemia, the anemia which may be present is readily alleviated by all the modes of therapy directed toward the leukemia. It is always gratifying to see the reciprocal rise in the red count as the white cells fall. Bleeding is rarely a problem since the platelet count is normal or even elevated for the greater part of the disease and infections are not seen as a rule until terminally, perhaps because of the quality of the white cells present.

A complication of chronic granulocytic leukemia which may necessitate early hospitalization is splenic infarction. This is associated with the massive splenomegaly which develops and may give rise to severe pain, fever, abdominal distention, and ileus. Therapy here is conservative with bed rest, analgesics, and antibiotics used as required. The agents used in the treatment of chronic granulocytic leukemia can be divided into two classes, (1) radiation, either in the form of roentgen ray or P^{32}, and (2) chemotherapeutic, such as urethane (ethyl carbamate), busulfan (myleran, 1,4 dimethane sulfonyloxybutane), triethylenemelamine (TEM), nitrogen mustard (HN2), or 6-mercaptopurine (purinethol, 6-MP). Mention should also be made of the two earliest chemotherapeutic agents, Fowler's solution and benzol, both of which have produced good remissions long before we entered the modern era of chemotherapy.

Initial treatment varies from clinic to clinic. Busulfan is the drug most popular with us at this time for initial therapy. In a dosage of 0.06 mg./Kg. daily, this drug

which comes in 2-mg. tablets, has produced excellent remissions. Response may come on slowly but it occurs quite regularly. As the white-cell count approaches normal, or if the fall in leukocytes is rapid, the drug is stopped or the dose reduced. Once a remission has occurred, therapy is discontinued. Thrombocytopenia is usually not a problem with busulfan unless larger doses than those recommended are used or the patient is particularly susceptible to the drug. Occasionally busulfan fails to reduce the splenomegaly despite a reduction of the white count to normal. It may be that not enough of the drug is used in such instances.

Many hematologists use roentgen-ray treatment to the spleen initially and busulfan subsequently. Doses of 150 to 300 roentgens to the spleen produce full remissions and, of course, rapid regression in spleen size. The number of visits a patient has to make while a remission is being established is less than the weekly visits required while the patient is on chemotherapy. This is of practical importance to the busy patient.

Radioactive phosphorus, sodium, and colloids of gold, zirconium, yttrium, manganese, and chromic phosphate have produced remissions in chronic leukemias but have no particular advantage over P^{32}. These isotopes deliver myelosuppressive radiation to the marrow and other sites where granulocytic elements are proliferating in much the same way that localized roentgen-ray therapy produces its response. P^{32} has the advantage of not causing radiation sickness but does require someone skilled and qualified in the handling of radioactive isotopes. It is administered intravenously in doses of 1 to 2 millicuries weekly for about 4 weeks with the trend of the white count being followed closely. A total course of not more than 4 to 6 millicuries is administered but therapy should be stopped when the count falls to about 30,000. About six months should elapse before additional isotope therapy is considered.

Other drugs such as nitrogen mustard, triethylenemelamine, Fowler's solution, and urethane have been used with excellent results. TEM is still a good drug for the treatment of chronic granulocytic leukemia. In doses of 2.5 to 5 mg./week it will lower the white count and reduce the size of the spleen; it is however, unpredictable in its action and sometimes produces a severe thrombocytopenia. Nitrogen mustard is effective but is too drastic an agent to use routinely. Occasionally it has produced temporary remissions in the terminal "blast crises" of granulocytic leukemia. Urethane is an excellent drug in chronic granulocytic leukemia. It is available in 0.3-Gm. enteric-coated tablets and has a good safety margin. It can be used in an initial dose of 1 to 3 Gm. daily which is reduced as the white-cell count falls. Maintenance therapy of about 1 Gm. daily may be given, or therapy stopped until relapse again requires its readministration. It may have some unpleasant gastrointestinal effects at times but this usually responds to decreased dosage or temporary cessation of the drug. Aplastic anemia, and liver necrosis, while reported, are quite rare. Fowler's solution given to the point of tolerance will produce excellent remissions and is still used.

In addition to the usual supportive measures such as antibiotics, transfusions, etc., the use of nitrogen mustard in the terminal "blast" crises of chronic granulocytic leukemia has been replaced by 6-MP (purinethol). Since the -blast phase is, in effect, a transformation into an acute stage, it does seem logical to use an agent which has proved to be successful in some cases of acute adult leukemia. The dosage used is identical to that used in acute leukemia.

Summary: It appears that chronic granulocytic leukemia may be successfully treated for much of its natural course, that initially, radiation to the spleen or busulfan therapy is indicated, that other agents can be used with almost as good results, and that terminally 6-MP may become necessary (Fig. 1). Supportive therapy throughout is of course a *sine qua non* of good management. Transfusions and antibiotics together with the

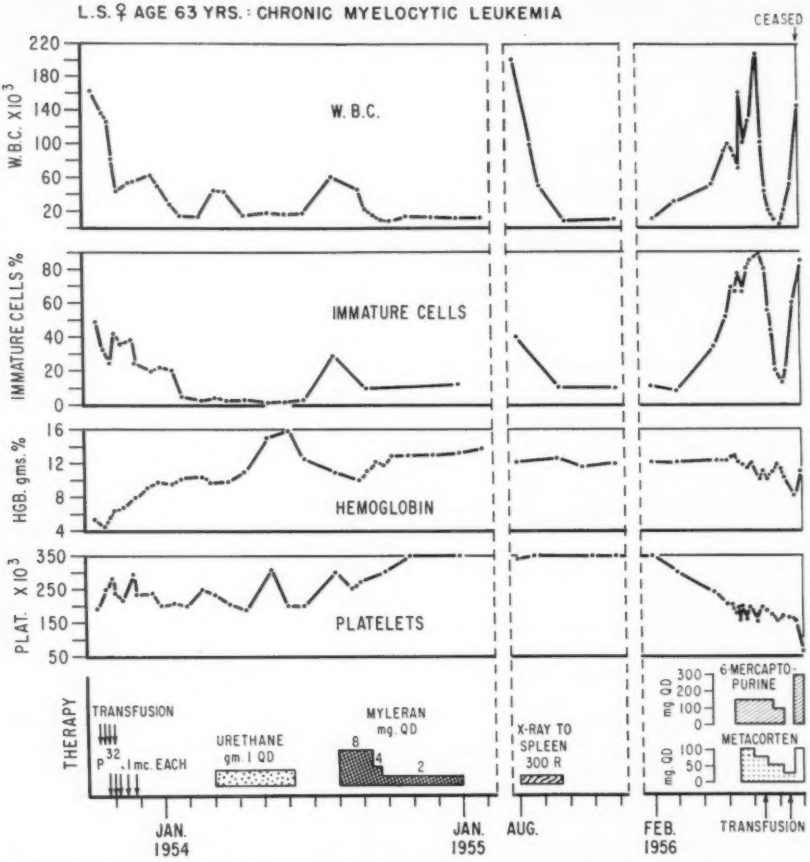


Fig. 1. Typical course and response to treatment of chronic myelocytic leukemia. Note the response to each agent used until the terminal -blast crisis.

agents noted above may sustain active useful life for many years.

Chronic lymphocytic leukemia is probably the most benign (with the longest survival) as well as the most common type of leukemia. The median survival is approximately 5.5 years but great variation in individual cases is to be noted. This disease in the older age groups may be mild and asymptomatic and appears to be a disorder entirely distinct from the more aggressive lymphocytic leukemia with marked lymphadenopathy, splenomegaly, wasting, and fever, which simulates a highly malignant lymphosarcoma.

The usual patient with this blood dyscrasia is over 50 years of age, more often a male than a female, and about 50 per cent of the cases present with lymph-node enlargement and moderate splenomegaly. The blood count reveals a mild or moderate normochromic anemia, a normal platelet count, a leukocytosis ranging from 10,000 to 200,000 with a lymphocytosis of 50 to 90 per cent consisting of a monotonous picture of small, mature lym-

phocytes. The bone marrow similarly is infiltrated with 50 per cent or more of these cells. In about a third of the cases the diagnosis is made by the chance observation of a mild lymphocytic leukocytosis with slight splenomegaly and/or lymphadenopathy during the course of a routine examination. An important point to remember, and one little emphasized, is that a lymphocytic leukocytosis even when accompanied by splenomegaly and bone-marrow infiltration of lymphocytes does not necessarily indicate an unequivocal diagnosis of chronic lymphocytic leukemia; such findings have been seen by us in carcinomas of the stomach, pancreas, adrenal, liver, and lung, in tuberculosis and in other chronic granulomatous diseases.

Since chronic lymphocytic leukemia may be a relatively mild disorder in elderly patients, they frequently die of intercurrent illness, such as heart disease, rather than of the leukemia. We have been following some patients with chronic lymphocytic leukemia in our clinic for over fifteen years. With progression and activation of the disease the white count tends to rise, the anemia becomes more severe, the spleen and lymph nodes enlarge, and the patient becomes resistant to therapy, with subsequent death from infection, anemia, or hemorrhage.

Complications which occur may be nonspecific (carcinoma, intercurrent infection, coronary disease) or part of the disease, such as the development of hemolytic anemia in 25 per cent of the patients, the occasional occurrence of agammaglobulinemia with an increased tendency to severe and prolonged infections, or thrombocytopenia with a variable bleeding tendency.

It has not been conclusively shown that any therapy of the chronic leukemias prolongs life and this is particularly true of the chronic lymphocytic variety. The object of treatment, therefore, is to improve the comfort and well-being of the patient for as long a period as possible. The therapeutic concept of "hands off" unless indicated is applied to the patient who is asymptomatic; we treat the patient and not the blood count. If a mild degree of anemia with weakness is present, supportive measures such as a nourishing diet, adequate rest, and occasional blood transfusions are prescribed. As a rule of thumb, local radiation is the first treatment of choice for the patient with localized enlargement of nodes and little or no systemic symptoms. A dosage of 100 to 300 r directed to the nodes is usually sufficient to cause reduction in their size. Spray irradiation is not recommended and radioactive phosphorus would seemingly have no advantages over conventional roentgen radiation. However, Osgood has recommended a "titrated dosage" of P^{32}, given at periodic intervals, not only for therapy of symptoms, but for prophylactic use. The patient with marked systemic symptoms such as fever, weight loss, severe anemia, etc., in addition to lymphadenopathy or organ enlargement may be treated with roentgen radiation to multiple areas or one of the mustards (alkylating agents) such as nitrogen mustard (HN2), triethylenemelamine (TEM), or chlorambucil (CB 1348). We prefer TEM in a dose of 2.5 to 5 mg. per week. This oral nitrogen mustard is given in a fasting state together with 1 Gm. sodium bicarbonate and a small amount of water. Breakfast is withheld for 2 to 3 hours. The white count is watched carefully during the next few weeks. If a more rapid response is required nitrogen mustard (HN2) may produce a gratifying remission in the usual intravenous dosage of 0.4 mg./Kg. given in 2 or 4 daily divided doses. Careful observation of the blood, bone marrow, and physical findings is necessary before additional therapy with either TEM or HN2 is prescribed. If thrombocytopenia is present and the bone marrow is diffusely infiltrated, these drugs must be used cautiously. Chlorambucil (CB 1348), a mild nitrogen-mustard derivative, is a relatively new drug. It is given orally in a dose of 0.1 to 0.2 mg./Kg. per day for a total dose of about 6.0 to 6.5 mg./Kg. in a course of 4 to 6 weeks. In chronic lymphocytic leukemia, it often produces as good a remission as the other agents although the response is usually

slower and the remissions may not be as complete. In general we have not found CB 1348 to be as good as TEM. The remissions produced by any of these agents are limited, and when one method of treatment no longer produces a response another has to be tried. Thus when roentgen-ray therapy fails to be effective, TEM or CB 1348 may produce a remission. Various agents may be used in sequence or in combinations to maintain a state of well-being for an increased period of time. But when none of these radiomimetic drugs or roentgen ray produces a response, the hormones are still available. Cortisone or ACTH are used for the frequently associated hemolytic anemia, when a hemorrhagic diathesis and thrombopenia are present or when all other agents have failed and non-specific stimulation might be helpful. The patient who is very sick when first seen, as well as one with a complicating hemolytic anemia, should receive these hormones from the start. The remissions produced by hormones are usually short-lived as compared with those which occur after roentgen ray, TEM, or chlorambucil. The usual methods of administering the hormones are followed: for the severely ill adult patient, hydrocortisone 100 mg., or ACTH 50 to 100 mg., or prednisone 20 to 80 mg. daily. Oral steroids in maintenance dosage may be given for many months.

Summary: Chronic lymphocytic leukemia is usually the most benign of all the leukemic processes. Treatment is not indicated unless there are symptoms; then, in addition to supportive measures, one has a choice of irradiation of the involved tissues, especially useful when the disease is relatively localized. HN2, TEM, chlorambucil, and roentgen ray or P^{32} may be used when there are systemic symptoms, and, in the patient who is very ill, or who has a superimposed hemolytic anemia or hemorrhagic diathesis, the cortisone group of drugs is effective (Fig. 2). The patients usually get along well during course of treatment. Life is probably not prolonged, but the well-being of the patient is enhanced by appropriate therapy.

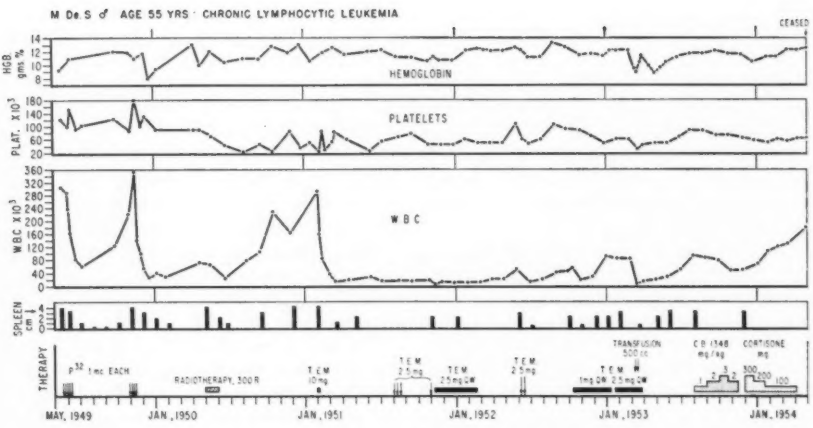


Fig. 2. Typical five-year course of chronic lymphocytic leukemia. Excellent response to P^{32}, roentgen radiation and TEM may be noted.

DOCTORS' DILEMMAS

Q *A 49-year-old white woman, gravida 3, para 3, noted the onset of occasional, bright blood in the stool after her last pregnancy eighteen years ago. The cause of the bleeding was diagnosed as hemorrhoids and sclerosing-solution-injection therapy was given seven years ago. The bleeding stopped at this time but has recurred during the past six months. Examination now reveals one enlarged hemorrhoid which is superficially eroded and bleeds readily when traumatized. There were no other significant findings on general examination. This patient has come to our diagnostic clinic for help. What would you suggest in the way of a diagnostic work-up?*

A Admittedly, the most likely diagnosis in this patient is recurrent bleeding of hemorrhoids but one cannot be certain that more important factors might not be the cause of rectal bleeding, e.g., a tumor of the colon. It is generally recommended that, prior to hemorrhoidectomies, a careful proctosigmoidoscopic examination be performed. It would be preferable to include a barium enema roentgen-ray study, especially if the proctosigmoidoscopic examination reveals blood in the lumen of the lower colon. Only too frequently a rectal surgeon sees patients who underwent hemorrhoidectomies for rectal bleeding and who returned six months later with persistent rectal bleeding and previously undetected, advanced cancer of the colon.

Q *I recently saw a 9-year-old boy who had an upper respiratory infection and concomitant cervical adenopathy. With antibiotic therapy there was prompt symptomatic relief and within one week the adenopathy disappeared. During the course of follow-up I have now discovered a 1-cm., moderately firm nodule in the left upper pole of the thyroid. The nodule moves on deglutition. I have not encountered a thyroid nodule in this age group before and I am wondering whether it may have any clinical significance.*

A Cancer of the thyroid must be included as a likely possibility in the differential diagnosis of thyroid nodule in this age group. Surgical consultation would seem to be indicated for further evaluation in order to establish a definite diagnosis. It may become necessary to perform an exploration of the thyroid region and excise tissue for histologic examination. Of course, prior to any contemplated surgery a complete and thorough medical work-up should be done with an evaluation of the physiologic status of the thyroid in terms of possible benign conditions.

Q *A 36-year-old white woman had a right radical mastectomy nine months ago for an infiltrating duct carcinoma, Grade II, with metastatic axillary lymph nodes. She was irradiated postoperatively and has remained free of recurrent disease*

except that one month ago she complained of low back pain. Roentgen-ray studies now show osteolytic metastases to the second, third, and fourth lumbar vertebrae. There is no evidence of recurrent tumor at the operative site and the chest roentgenogram is normal. This patient is gravida 3, para 3, and is actively menstruating. What method of therapy would you deem most advisable in this clinical setting?

A Since this patient is currently having normal menses, the most likely form of therapy would be castration either by surgical or radiation methods. The purpose of castration would be to remove a source of endogenous estrogen. Subsequent measures would naturally depend upon the response to castration and might include male hormone therapy, regional roentgen-ray therapy to the site of painful metastasis, adrenalectomy, and perhaps hypophysectomy.

Q *A 52-year-old male factory worker came to my office complaining of a lump in the left breast which was first noted about two months ago. The mass is not tender, fairly well circumscribed, located immediately beneath the areolar margin and measures about 2 cm. It is moderately firm and seems to be stuck to the nipple. There is no nipple discharge. Does this suggest a benign fibroadenoma that could be observed without specific therapy?*

A Many leading tumor pathologists agree that a true fibroadenoma is rarely, if ever, encountered in the male breast. In view of the patient's age, location of the mass, and description of fixation to the overlying nipple, one must consider the possibility of cancer of the male breast. On the basis of the physical findings it would seem advisable to perform biopsy of the mass in order to determine adequately a diagnosis of gynecomastia, or a malignant tumor, and then recommend treatment according to histologic appearances.

Q *One week ago I saw a 2-year-old girl whose mother, for six months, had noticed a slowly enlarging mass on the left buttock. The mass is 5 cm. in diameter, moderately firm, not tender, and is not attached to the skin. The child is in apparently good health at present and the past history shows a normal growth and development pattern. Would you consider surgical removal of the mass in a child of this age, or would you recommend observation only?*

A The history of progressive increase in the size and the location of the mass would make one think of the possibility of a soft-tissue sarcoma. It would seem advisable to remove this mass without delay so that an accurate histologic diagnosis might be obtained and appropriate treatment instituted.

Q *A 47-year-old white woman came to our clinic complaining of a lump in the right breast. Four weeks ago she was injured by a toy thrown by her child and developed a "black and blue mark" at the current site of the lump. The discoloration of the skin has since disappeared, leaving the underlying mass, which the patient thinks is getting smaller. The mass now measures 5 x 4 cm., is rather firm and is not attached to the skin. Upon examinaion the opposite breast, both axillas, and the supraclavicular areas were found to be normal. Would you recommend surgical removal of the lump in the breast?*

A The history and physical findings are strongly suggestive of fat necrosis at the site of the trauma. One might be inclined to observe this patient at weekly intervals to determine whether the mass is really getting smaller. If there is definite diminution in size, one might expect the existing mass to disappear without specific therapy. If, however, there is no change in size or consistency of the mass within two or three weeks, a formal biopsy should be done without further delay to rule out a diagnosis of cancer of the breast.

new developments in cancer

Endocrine Test . . .

University of Chicago investigators have expressed satisfaction with a new test for residual pituitary function after hypophysectomy. They label cholesterol with radioactive carbon or tritium, inject or feed it to patients, and examine the urine for radioactivity incorporated in progesterone or cortisone-type steroids. If the test is positive, they can be sure that functional endocrine tissue remains. The test has been made possible by a liquid scintillation counter developed at Los Alamos and the University's Institute for Nuclear Studies. The test substance is mixed with chemicals that fluoresce in the presence of radiation. The test is of particular value here where hypophysectomy has been achieved in more than twenty-eight patients by seeding the pituitary with tiny grains of radioactive yttrium implanted through a small hole in the skull. All of the patients were women with far-advanced and widely metastatic cancers of the breast. The majority of them have been helped by the method. The scientists conducting the experiments include Doctors George V. LeRoy, M. Edward Davis, and David Ruml.

Lupus Mechanism . . .

Investigation into the phenomena of cell aging has produced an interesting lead to the control of lupus erythematosus. The studies were done by Nathaniel B. Kurnick at UCLA and the Long Beach V. A. Hospital. Lupus erythematosus appears to be caused by a rapid aging and death of cells and the production of allergic antibodies against the cell debris. The aging process is indicated by the presence of large amounts of DNase and little DNase inhibitor, the reverse of the situation found in young growing cells. Dr. Kurnick discovered in test-tube experiments that DNase inhibitor (abundant in some white cells) reversed the lupus process. In tests on sixteen patients long and gravely ill with lupus erythematosus (they were injected intramuscularly with DNase-inhibitor–containing white cells), treatment appeared to be uniformly good. Within one week, the skin lesions of all patients cleared; and within six weeks pains around the joints, muscles, hearts, and lungs disappeared. The studies were made in systemic lupus erythematosus, not chronic discoid lupus, a disease of the skin alone.

Cortisone Mechanism . . .

Some advance in understanding one of the major mysteries of biochemistry—how a hormone works—may have been made in work by Theodore B. Schwartz, of Presbyterian Hospital and the University of Illinois Medical School, Chicago. Preliminary evidence suggests that hormones may work with or through peptidases in assembling or dismantling the protein molecule. Various peptidases are known to disengage specific or terminal amino acids in peptides comprising the protein chain. The Illinois scientist measures the peptidase activity of rat-diaphragm culture. He has found that the diaphragms of rats highly dosed with cortisone have very great peptidase activity, while the diaphragms of adrenalectomized animals have virtually no peptidase activity. Because cortisone is ineffective when added to cultured diaphragm, Dr. Schwartz has concluded that its influence on peptidase is exerted through other systemic mechanisms.

Cancer Phobia . . .

Dr. David A. Wood (U. of Calif., President of the American Cancer Society) has reported that cancer phobia in the United States is diminishing. He said a 1948 survey of the attitudes of psychiatrists and general practitioners toward the Society's educational program showed 11.4 per cent regarded the program as definitely harmful. In a second survey seven years later this figure fell to 6.5 per cent. About two-thirds felt no psychological harm had been done; and about 85 per cent believed either no harm was done or the benefits outweighed possible disadvantages. Psychiatrists may be presumed to be more concerned about mental trauma than the value of early detection. Dr. Wood paid tribute to science news writers for "doing a responsible job in informing the public of the many problems and moderate progress in cancer research." "They are ably interpreting scientific progress without stirring up false hopes," he added. "By their judicious reporting they have kept within control the unfounded fears and phobias of cancer."

"Growing Up" Hormone . . .

Scientists at Louisiana State University have found that pupation hormone, which controls metamorphosis in fruit flies, controls the growth of the large pigmented tumors that some of the flies exhibit. They observed that flies lacking a normal ring gland (situated near the mouth) that produces the hormone developed the tumors. Flies with functional ring glands didn't. When the flies were given the hormone during their change to the adult form, they built hard, restraining capsules around the tumors. These inhibited tumors resumed growth when they were removed from the flies and placed in a culture lacking the hormone. In some respects, pupation hormone resembles thyroid hormone, which controls the metamorphosis of salamanders and other species. The experiments were done by C. H. Haddox, Jr., with the collaboration of Walter Burdette, now at the University of Missouri.

Chemotherapy of Lung Cancer . . .

A University of California group has proposed that, in view of the discouragingly low cure rates achieved by surgery and radiation, greater emphasis be placed on experimental chemotherapy for lung cancer. They contend that in too many cases "successful" surgery has made respiratory cripples of patients and may have shortened their lives. The group is composed of Drs. Roger Wilson, Seymour M. Farber, David A. Wood, and Orville F. Grimes. The investigators have recommended that patients be given a battery of tests preoperatively as a safeguard. These include tests for ventilation, diaphragm weakness, heart disease, emphysema, oxygen consumption, gas mixing and blood acidity, oxygen and carbon dioxide content. Where the surgeon is competent to undertake the test, it would be ascertained whether the prospective surviving lung is capable of sustaining the patient.

Li (U. of Calif.) has decided growth hormone is inaptly named. Now armed with ample experimental quantities of pure human pituitary growth hormone, he has found the substance important or essential to reproduction, lipid and carbohydrate metabolism, and immunity -- rats treated with growth hormone had triple the antibody titer of untreated animals. Growth hormone, earlier shown by others to be necessary for certain carcinogen-induced cancers and shown by Li to cause widely scattered cancers, plays a prominent role in lactation and breast development, Li and Lyons learned.

Duran-Reynals (Yale) has tied together viruses, hormones, and carcinogens. With cortisone, either of two viruses (vaccinia or dermo), and methylcholanthrene in very low, sub-carcinogenic doses he produced cancers in mice. All three were required. Estrogen inhibited the cocarcinogenic effect of cortisone by building up mesenchyme which cortisone depressed.

Leblond (Montreal) and Everett (U. of Wash.) measured the differential growth of tissues by giving rats radioactive methionine and at 4, 24, and 36 hours testing for uptake. The autoradiographs showed amazing synthesis by the pancreas -- this enzyme factory completely renewed itself every 36 hours. It was three times as dynamic as the liver and four times as active as the kidney, skin, hair, and nails. Intestinal mucosa, as expected, also turned over rapidly. Thyroid hormone accelerated synthesis for most tissues. Even teeth were found to incorporate substantial dentine during observation.

Kidd and others (Cornell) are seeking to isolate a potent "Factor X" in guinea-pig serum that completely cures two experimental mouse lymphomas which are unaffected by conventional drugs and roentgen rays. Only guinea-pig serum contains the factor -- human, horse, rabbit, and other sera were inactive. Factor X was effective only on these two tumors. At this stage, enormous quantities of serum must be given intraperitoneally for effective mouse treatment.

Neurath (U. of Wash.), in the most recent of a series of important enzyme observations in his laboratory, reports that at least some enzymes catalyze in a two-step operation. He has identified the two surface sites of enzyme attachment to, and release from, substrate. Earlier work with Vallee (Harvard) has yielded a simple, rapid, cheap equip-

ment for measuring blood content of zinc-containing enzymes.

Fink (U. of Colo.) has shown relationship between serotonin and anaphylaxis. She found serotonin 1,000 times as potent as histamine in inducing anaphylactic shock in sensitized mice.

Barker and others (U. of Ala. Medical School) have tested in vivo and in vitro the effect of thyroid on metabolism of various tissues. Sensitive to thyroid stimulation were liver, kidney, skeletal muscles, and heart. Unresponsive were brain, spleen, ovaries, uterus, testes, gastrointestinal smooth muscle, prostate, and seminal vesicles.

Argus, Hewson, and Ray (U. of Fla.) injected control and tumor-bearing mice with FDSN, or fluorene-2,7-di-(sulfonamido-2'naphthalene)-S^{35} and found that non-cancerous controls concentrated 8 times as much FDSN in spleen reticuloendothelial tissue as could be found in similar tissues of animals bearing stomach- and breast-cancer transplants. Liver differential was not so pronounced. The phenomenon became apparent about three weeks after transplant.

Lerman (U. of Colo.), utilizing his own and Puck's exquisite techniques, has moved another step forward in identifying genes. It now looks as though there may be several (perhaps three or more) genes per DNA molecule.

Kinosita and Ohno (City of Hope) are finding with considerable consistency a forty-first chromosome in the mouse leukemic cell. Their dramatic movies on the "birth" of blood cells are adding a new dimension to hematology and scientific education.

Greenberg (U. of Calif.) has worked out roughly the major steps in methylation of pyrimidines and is testing, among others, a diazouracil as a potential thymine antagonist. This type of compound elsewhere has shown carcinostatic effects in mice but behaves like a hallucinogenic drug in man.

Luria and his group (U. of Ill.) continue to make rapid progress in their fascinating studies of "infectious heredity." They have shown that salmonella-phage virulence can originate by a series of mutations blocking various chemical steps required for latency. Transduction (transmission of genetic properties from one cell to another) can be accomplished with DNA equivalent to that of a phage particle. In these studies, the word mutation is nearing a definite chemical equation. (To be continued in next issue.)

COMING MEDICAL MEETINGS

Date 1957	Meeting	City	Place
April 29-May 2	International Academy of Proctology	New York City	Plaza Hotel
May 5-8	Aero Medical Association	Denver, Colo.	
May 5-10	International Congress of Otolaryngology	Washington, D. C.	Hotel Statler
May 12-13	International Congress of International Society of Bronchoesophagology	Philadelphia	
May 14-17	International Cancer Campaign Symposium on Biochemistry of Cancer	London	
May 15-17	American College of Cardiology	Washington, D. C.	Hotel Willard
May 17-18	American Gastroenterological Association	Colorado Springs, Colo.	Broadmoor Hotel
May 19-24	National Conference of Social Work	Philadelphia, Pa.	
May 27-29	American Gynecological Society	Hot Springs, Va.	The Homestead
May 29-June 2	American College of Chest Physicians	New York City	Hotel Commodore
May 30-31	American Geriatrics Society	New York City	Waldorf-Astoria
May 30-June 1	American Radium Society	Quebec, P.Q.	Chateau Frontenac
May 30-June 1	The Endocrine Society	New York City	Hotel New Yorker
May 30-June 2	American Therapeutic Society	New York City	Essex House
May 30-June 2	American Medical Women's Association	New York City	Barbizon Plaza Hotel
June 1-2	Society for Investigative Dermatology	New York City	Belmont-Plaza Hotel
June 3-7	American Medical Association	New York City	
June 4-6	International Therapeutic Congress	Utrecht, Netherlands	
June 17-21	Canadian Medical Association	Edmonton, Alberta	
July 1-6	International Congress on Occupational Health	Helsinki, Finland	
July 9-11	International Society of Geographical Pathology	Paris	
July 14-19	International Gerontological Congress	Merano-Bolzano, Italy	
July 15-19	British Medical Association	Newcastle upon Tyne, England	
July 15-20	International Congress of Clinical Pathology	Brussels	
July 24-29	International Congress of Nutrition	Paris	
July 31-Aug. 6	International Congress of Dermatology	Stockholm	
Aug. 26-31	Congress of the European Society of Haematology	Copenhagen	
Aug. 28-Sept. 3	Congress of International Society for Cell Biology	St. Andrews, Fife, Scotland	
Sept. 9-20	International Conference on Radio-Isotopes in Scientific Research	Paris	
Sept. 29-Oct. 5	World Medical Association	Istanbul	
Oct. 1-4	American Roentgen Ray Society	Washington, D. C.	Shoreham Hotel

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